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Danish Atomic Energy Commission
Research Establishment Risø

Proceedings of The Third International
Meeting on The Toxicity of Thorotrast,
held at The Finsen Institute,
Copenhagen 25-27 April 1973

Sponsored by The Danish Atomic Energy Commission, The National
Health Service of Denmark, and The World Health Organization

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World Health Organization**

**Editor
H. Faber**

Abstract

These proceedings contain thirty-one papers presented at the "Third International Meeting on the Toxicity of Thorotrast". The papers are arranged according to the following subjects: Physics and Dosimetry of Daughters, Biological Effects, Follow-up and Epidemiological Surveys including Human and Experimental Carcinogenesis.

CONTENTS

	Page
Introduction J.S. Mitchell	7
Tissue Distribution and Steady State Activity Ratios of Th 232 and Daughters in Man Following Intravascular In- jection of Thorotrast A. Kaul	14
Radiation Dose in Lungs R. Grillmaier, H. Muth	31
Mean Organ Dose Rates in Man Following Intravascular In- jection of Thorotrast A. Kaul	40
Assessment of Organ Distribution of Thorium by Neutron- Activation-Analysis H. Wesch, H. Kampmann, K. Wegener	52
The Retention of the Daughters of Thorium 232 in the Soft Tissue in Animals C. Trolle	61
Distribution of Thorotrast and its Daughter Nuclides and Estimation of Absorbed Dose in the Human Organs S. Okawara	72
Thorium Series Radionuclides in Compact Bone of Thorotrast Cases - Results of Measurements at IAEA R.A. Dudley	81
The Skeletal Dose from 224 Ra Following Intravascular Ad- ministration of Thorotrast R.E. Rowland, J. Rundo	95
Chromosome Aberrations Caused by Thorotrast W. Kemmer, H. Muth, F. Tranekjer, U. Borkenhagen	104
The Edinburgh Thorotrast Series - Report of a Cytogenetic Study K.E. Buckton, A.O. Langlands	114
Followup of Thorotrast Patients from Boston, Massachusetts and Ann Arbor, Michigan, U.S.A. M.L. Janower	126
Follow-up of Danish Thorotrast Cases M. Faber	137

	Page
Statistical Problems of Thorotrast Studies	
H. Immich	148
Development and Improvement of the Questionnaires	
P. Schmidlin, G. Wagner	151
Actual Status of the German Thorotrast Study	
G. van Kaick, K.E. Scheer	157
Special Clinical Findings among Thorotrast Patients	
G. van Kaick, D. Lorenz, I. Drings	163
Medical Problems Concerning the Control Group	
D. Lorenz, W.J. Lorenz, G. van Kaick	169
Thorotrast Injury in Japan	
T. Mori, Y. Mozue, T. Miyazi, S. Takahashi	175
Epidemiological Follow-up Studies of the Portuguese Thorotrast Series (up-dated Results)	
J. da Silva Horta, L. Cayolla da Motta, M.H. Tavares ...	193
Liver Studies in the Thorotrast Patients - Laboratory and Clinical Findings (Study of 175 Cases)	
M.H. Tavares, A. Saragoca, J. da Silva Horta	212
Liver Ultrastructural Findings in Patients Injected with Thorotrast	
J. da Silva Horta, M. Luisa Cristina, A.S. Baptista	219
Tumours Developed in People Injected with Thorium Dioxide (Thorotrast) (Portuguese Experience)	
J. da Silva Horta	233
Pathological Findings in the Res (Liver, Spleen, Lymph Nodes, Bone Marrow) of Thorotrast Patients (Histological and Autoradiographic Investigation)	
K. Wegener, H. Wesch, H. Kampmann, R. Zahnert	248
Historadiographies and Autoradiographies from Pieces of Organs of People Injected Systemically with Thorotrast	
J. da Silva Horta, J. Moura Nunes	259
Thorotrast-induced Spindle Cell Sarcoma and Hepatic Cholangiocarcinoma in Syrian Hamsters	
T. Mori, T. Okamoto, M. Umeda, K. Saito, H. Okanzima ...	267
Non-Radiation Effects of Thorotrast and other Colloidal Substances	
W. Riedel, B. Müller, A. Kaul	281
The Effect of Thorotrast Enriched with Th 230	
M. Faber	294

	Page
The Stability of Leukemogenic Risk in Human Marrow Irradiated by Rays L.D. Marinelli	303
Dose Effect Relations in Hepatic Carcinogenesis M. Faber	308
Aspects of Collaboration Relating to Follow-up-Studies H. Immich	317
Expected Late Effects in Thorotrast Patients H. Muth, E. Oberhausen, R. Kunkel, U. Herzfeld	320
Concluding Discussion	330
Cases of Bone Tumors in Thorotrast Injected Patients, Portuguese Material, (Later Information)	333
List of Participants	334

Introduction

by

J.S.Mitchell

Addenbrooke's Hospital, Cambridge, England.

After more than 40 years, one can talk about history. Colloidal thorium dioxide was introduced as a radiological contrast medium in about 1928. The most important preparation is Thorotrast which was developed for intravenous injection and has been used widely since 1931.

The story of Thorotrast is a sad and salutary one, but I suggest very relevant to medicine at the present time. Thorotrast was obviously an outstandingly good radiological contrast medium with practically no immediate toxicity. Nevertheless, despite warnings about the risks of the late effects of its radioactivity, its use in diagnostic radiology spread widely and continued for many years apparently everywhere. In the J.A.M.A. of December 24th 1932 (Vol.99, pp.2183-2185) an unambiguous report was published by the Council on Pharmacy and Chemistry. After considering the available evidence including that of H.S.Martland on radium poisoning and specifically mentioning "the short period during which patients have been kept under observation", "the Council voted that Thorotrast be not accepted for intravenous administration". It also expressed reservations about its uses in retrograde pyelography and for outlining various body cavities. Further, in 1934 and 1936 in Paris, Rousay, Oberling and Guérin showed that Thorotrast produced sarcomas easily in white rats at the site of injection, both intraperitoneal and subcutaneous. This was an accidental finding in

rats surviving about a year after injections of Thorotrast, which had produced regression of transplanted Jensen sarcoma and Flexner-Jobling carcinoma. Some of the tumours arose in relation to Thorotrast granulomata. Many experiments were carried out, which established a causal relationship, the frequency of sarcoma induction increasing with the amount of Thorotrast injected.

Since then and mainly since the War, a large number of reports have appeared of late deaths usually 20 years and longer after administration of Thorotrast, mainly including single cases or a few cases of malignant liver tumours - not only malignant haemangio-endothelioma but also malignant cholangioma and hepatoma -, malignant tumours of some other organs and fatal blood dyscrasias, chiefly leukaemias and aplastic anaemias, together with local granulomata. A very good bibliography has been published by the International Atomic Energy Agency (1964).

The Finsen Laboratory in Copenhagen has played a leading part in the systematic epidemiological study of Thorotrast. In 1948, the question was raised whether some cases of obscure illness were due to the late toxic effects of Thorotrast. The Director, the late Dr.O.M.Henriques, realized the importance of the Thorotrast problem and must be given great credit for organizing the first collection and investigation of a large number, 234, patients who had received Thorotrast injections, with a view to long-term follow-up. He emphasized the relevance of the uptake of the colloidal

thorium dioxide into the reticulo-endothelial system after intravenous and intra-arterial injection and in 1953 presented a Finsen Laboratory Report entitled "Radiation induced dysaemia - Review of 234 patients with deposits of $0.5 - 5 \mu\text{C Th}$ ". He said in the introduction "These investigations are not only a team work, they are part of an Olympic race ... We must hope that our basic work has been sufficiently accurate, comprehensive and extensive for our successors to win when carrying the torch the last miles". Soon afterwards on 2nd August 1953 Oscar Henriques died. The good work has certainly been carried on at the Finsen Laboratory by Professor Mogens Faber. In 1966 he reported "A follow-up of 1000 Thorotrast cases in Denmark" (Faber, 1968) and much more evidence has been collected since then.

It may be of interest to say a few words about the work here in the early days. Dr. Henriques with characteristic enthusiasm obtained help and collaboration from the British Medical Research Council and the U.K. Atomic Energy Research Establishment, Harwell. At his request, I spent some time here under the auspices of the M.R.C. My wife, Dr. L. Mary Mitchell, and I had the privilege of joining the team and we certainly worked very hard. I wrote a 58 page report (MRC 51/548). Most of the staff could devote only part-time work to the Thorotrast investigation. The

pathologist and haematologist was Dr. Charles Johansen. In 1955, he reported on a "reticulo-endothelial sarcoma in rabbits provoked by intravenously deposited thorium (Johansen, 1953a, b). Dr. O.G. Backer (1956, 1958) carried out extensive haematological studies. "The physical and technical parts of the work", especially the total body radioactivity measurements, were carried out by Mr. (now Professor) P.G. Jensen and Dr. A.H. Ward, a physicist seconded from Harwell. He was succeeded by Dr. J. Rundo who correlated the total body γ -ray activity measurements on the patients with measurements on a realistic phantom and calculated the radiation dose in rads in various tissues and organs. Professor J. Rotblat, Dr. G.B. Ward and Dr. G. Hjort studied autoradiography. Great attention was paid to the problems of evaluation of tissue dose in individual patients. We shall hear to-day about the recent developments in this field.

In the last 20 years, a number of other surveys and epidemiological studies of Thorotrast patients, and a wide range of experimental investigations have been carried out throughout the world. May I emphasise the value of collaboration between groups in this type of work. This meeting provides a great opportunity both for assessing the present position and for looking to the future. In concluding this introduction, may I thank Professor Mogens Faber on behalf of all of us for arranging this conference.

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Tissue Distribution and Steady State Activity Ratios of
Th²³² and Daughters in Man following intravascular
Injection of Thorotrast*

by

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Abstract

Published data and results of own investigations on tissue distribution and steady state activity ratios of Th²³² and daughters in man were compiled in order to get "best estimates" for dose rate calculations in patients with long-term Thorotrast burdens.

According to the results about 95 % of intravascularly injected colloidal ThO₂ are retained by the organs of the reticulo-endothelial-system (RES) of the "standard Thorotrast patient" (liver: 59 %; spleen: 26,5 %; bone marrow: 9,3 %). Only 0,7 and 0,1 % are distributed within the lungs and the kidneys, respectively. The fractional retention of Th²³² in the marrow-free skeleton proved to be 4 % on the average.

Due to recoil at the moment of their creation by decay thorium daughters are able to escape from the ThO₂ aggregates in order to be translocated to other organs or to be excreted from the body. Consequently the activity ratios between daugh-

* Dedicated with Gratitude to Prof. Dr. B. Rajewsky on his 80th Birthday

ters and Th^{232} in tissues of Thorotrast patients are quite different from those in sealed Thorotrast ampoules of the same age. Thus, in cases of long-term Thorotrast burdens, Ra^{228} is only up to 40 % in equilibrium with its parent Th^{232} in organs of the RES, and in excess to Th^{232} in marrow-free bone in the order of 20 %. The same proves true for Ra^{224} , which is eliminated from the Thorotrast deposits of the RES and partly translocated to the marrow-free skeleton. The corresponding activity ratios between Ra^{224} and Th^{232} yielded 0,25 - 0,36 for the liver, spleen and bone marrow, and proved to be almost 2 for the marrow-free skeleton. In the lungs Pb^{212} is assumed to be in excess to its parent Ra^{224} by a factor of nearly 20, due to Pb^{212} bound to the cellular fraction of blood, and due to decay of Rn^{220} having been escaped from the RES into the general circulation.

The average steady state activity ratios of Th^{232} within the RES of the "standard Thorotrast patient" proved to be quite comparable to those observed in animal experiments, indicating the elimination of Th^{232} decay products in vivo from ThO_2 aggregates to be a property of Thorotrast itself rather than of the animal.

Introduction

Patients with Thorotrast body burdens constitute a significant population for epidemiological studies on the effects of chronic internal irradiation. However, in addition to clinical examinations, information on the associated radiation energy absorbed is necessary if these studies are to yield results of general usefulness.

Unfortunately, Thorotrast radiation dosimetry is a problem of great complexity. This is, in part, due to the colloidal nature of $\text{Th}^{232}\text{O}_2$, and the large number of different radio-nuclides which constitute the Th^{232} decay series, and will exhibit its own characteristic metabolic behaviour within the body. Because of this different movement of Th^{232} and its daughters as well as their inhomogeneous distribution in several different physical phases of the injection material radioactive equilibrium will not exist within the body tissues. Moreover, non-uniform distribution of the thorium colloid in

tissues as well as self-absorption of emitted radiation due to aggregation of the ThO_2 particles within the living tissues also serve to complicate dose calculations.

During the past years various investigators have concerned with extensive investigations on the distribution and metabolic pathways of Th^{232} and its longer lived daughters in Thorotrast patients as well as in animals, as a basis for estimating absorbed doses (ROTHBLAD et al., 1953; RUNDO, 1956; 1957; 1958; 1960; HURSH et al., 1957; HURSH, 1965; REYNOLDS et al., 1957; MARINELLI et al., 1962; 1963; HEYDER, 1968; KAUL, 1964; 1965a; 1965b; 1965c; 1969; 1971; KAUL et al., 1969; 1970; MUTW et al., 1962; OBERHAUSEN et al., 1964). The metabolic pattern of behaviour of the short-lived thorium daughter Rn^{220} was extensively studied in man particularly by RUNDO et al. (1958), GRILLMATER (1964), GRILLMAJER et al. (1964), KAUL (1964), and HURSH (1965; 1966).

On the basis of published data and those of own investigations PARR and co-workers (1969) summarized some of the currently accepted data on Thorotrast metabolism with particular consideration of the metabolism of the shorter-lived Th^{232} daughter products Ac^{228} , Ra^{224} , Pb^{212} , and Bi^{212} .

Similarly to these authors it is the aim of the present study to derive from published data and those of own investigations present "best estimates" on tissue distribution and steady state activity ratios of Th^{232} and daughters in man, and to compare the results with those of own animal experiments and those of others.

Results

1. Tissue Distribution of Th^{232} in Man

In table 1 average concentrations of Th^{232} in various organs of Thorotrast patients are summarized from results of tissue analyses of 30 patients published up to now. According to PARR et al. (1969) the concentrations of Th^{232} in the tissues have been normalized with respect to the Th^{232} content of the liver, for being able to extrapolate the average tissue distributions to the whole body under constant conditions. The results indicate the average Th^{232} concentration in the spleen, of Thorotrast patients to be approximately 500 % of that in the liver.

The concentration of Th^{232} in the bone marrow and bones containing marrow proved to be 18 % on the average while that in marrow-free bone, the kidneys, and the lungs yielded 1 to 2 % of that in the liver. Published data on Th^{232} concentrations in kidney samples of patients with retrograde Thorotrast pyelography and those in perivascular deposits were not compiled, because the injection conditions are hardly to be compared to those of usual intravascular applications of colloidal ThO_2 .

In order to get present "best estimates" of the organ distribution of Th^{232} in a "standard Thorotrast patient" after intravascular injection of Thorotrast, extrapolations from the average data on Th^{232} tissue distribution of table 1 for man to the whole body had been made for the Standard Man. The results are summarized in table 2, indicating a fractional retention of Th^{232} in the liver of about 60 %. The average Th^{232} content of the spleen proved to be 25 %, and that of the red bone marrow about 9 %, relative to the amount within the whole body. In the total marrow-free skeleton less than 4 % of whole body Th^{232} are retained, while the corresponding distribution in the lungs and kidneys is below 1 %. Amounts of Thorotrast contained in other organs are assumed to be negligible. As relevant data on the fractional retention of Th^{232} in lymph nodes are lacking no estimate of the amount of Thorotrast in the whole lymphatic system has been done.

In table 3 the calculated average organ distribution of Th^{232} in man is compared to results of former own estimates or those published by others. Generally, the data are in rather good agreement, indicating about 95 % of whole body Th^{232} to be retained by the RES in cases of intravascularly injected Thorotrast into patients.

2 Steady State Activity Ratios between Thorium Daughters and Th^{232} in Tissues of Thorotrast Patients

According to the above remarks further presupposition for estimating dose rates in organs of Thorotrast patients is the knowledge of the steady state activity ratios between thorium daughters and Th^{232} in tissues of man.

Concerning the activity ratios between the longer-lived thorium decay products, i.e. $\text{Ra}^{228}/\text{Th}^{232}$, $\text{Th}^{228}/\text{Ra}^{228}$, and

Ra^{224}/Th^{228} , in tissues belonging to the RES, quite relevant data from a larger number of carefully analyzed Thorotrast cases are available from literature. Equilibrium activity ratios of Th^{232} daughters in liver, spleen, and bone marrow including bone containing marrow, as well as in marrow-free bone have been compiled from literature or calculated from published activity data for long-term Thorotrast burdens, and summarized in tables 4 - 7. Average values of the activity ratios of tissue samples of 10 - 27 individual cases are included in the tables in a qualified sense that those ratios which were felt to be obviously consistent with the majority of published data were not taken into consideration.

Concerning the equilibrium activity ratio between Pb^{212} and Ra^{224} only few data are available for man, particularly for bone marrow and marrow-free bones. This proves true above all for the ratio Bi^{212}/Pb^{212} which was determined in only 2 human samples of spleen tissue.

For the lungs and kidneys of patients with intravascularly administered Thorotrast data on steady state activity ratios between thorium daughters and Th^{232} are only known at present from investigations of PARR and co-workers (1969) in 4 patients with Thorotrast burdens between 26 days and 26 years. Though these data may hardly be assumed to be of general relevance, average values have been estimated from the different activity ratios, being summarized in tables 8 and 9.

Similarly to the above procedure of calculating present "best estimates" of the tissue distribution of Th^{232} in the body of a "standard Thorotrast patient" present "best estimates" of steady state activity ratios in patients with long-term Thorotrast burdens after intravascular injection of the ThO_2 colloid were performed as was done earlier by PARR and co-workers in 1969. The results having been summarized in table 10, again elucidate the absence of relevant data on Bi^{212}/Pb^{212} activity ratios in most tissues of man.

Within organs belonging to the RES, i.e. the liver, spleen, and bone marrow, distinct radioactive disequilibrium exists between Ra^{228} and its parent Th^{232} , according to a continuous wash-out of the long-lived radium isotope which proved to be 60 % according to own animal experiments with rabbits (KAUL,

1969; KAUL et al., 1969). The same proves true for Ra^{224} which is obviously eliminated from Thorotrast deposits within the liver, spleen and bone marrow to a less extent compared to Ra^{228} , as can be seen from the corresponding activity ratios Ra^{224}/Th^{228} . Again from animal experiments we know that only 35 % of Ra^{224} being created by decay of Th^{228} is released from ThO_2 deposits within the liver and spleen (KAUL, 1969; KAUL et al., 1969). This reduced elimination of Ra^{224} is more likely due to the higher recoil energy of 97 keV of Ra^{224} at the moment of its creation (by α -decay of Th^{228}) compared to that of Ra^{228} (70 keV), and in pursuance of which, due to a higher probability of being retrapped by surrounding ThO_2 particles of the aggregates. The shorter half-life of Ra^{224} is probably of less importance, as we know from animal experiments, that the biological half-life of radium in ionic form within the liver and spleen of rabbits is only about 6 hours (KAUL, 1969).

In marrow-free bone Ra^{228} and Ra^{224} have been found to be in excess to their parents due to translocation, in part, of both radium isotopes, mainly from the liver and spleen to bone. This process, first carefully studied in 1957 by REYNOLDS and co-workers, had been investigated in Thorotrast rabbits, and formally described by means of a compartment model, revealing 15 % of Ra^{224} , being eliminated from the RES, to be translocated to the entire skeleton of the animals (KAUL, 1969; 1971; KAUL et al., 1970). The excess of Pb^{212} compared to Ra^{224} by a factor of approximately 18, as published by PARR et al. (1969) for only one sample of lung tissue, is due to Pb^{212} bound to the cellular fraction of the blood, and due to decay of Rn^{220} , having been escaped from the RES into the general circulation in the order of 16 or 20 %, according to HURSH (1965) and GRILLMAIER et al. (1964), respectively.

The average steady state activity ratios of Th^{232} daughters within the RES of the "standard Thorotrast patient" of table 10 prove to be quite comparable to those observed in own animal experiments (HEYDER, 1968; KAUL, 1969) and those published by PARR et al. (1969), indicating the mechanism of elimination of Th^{232} decay products in vivo from ThO_2 aggregates to be a property of Thorotrast itself rather than of the animal (see table 11). The corresponding mechanism, having been shown to be

most adequate to predict elimination of thorium daughters from ThO_2 particles in vitro as well as in vivo is that of escape of thorium decay products by recoil at the moment of their creation. This recoil model had been developed by PARR (1965), and was applied later to interpretations of results of own investigations (KAUL, 1969; HEYDER et al., 1971).

For the whole body, estimates of the steady state activity ratios have also been done on the basis of average tissue equilibrium activity ratios of table 10, by attaching weighting factors according to the organ distribution of Th^{232} as derived above (see table 2). The results of these calculations, summarized in table 12, prove to be quite comparable to those estimated from excretion analyses, as obtained by different authors (HURSH et al., 1957; RUNDO et al., 1958; MUTH et al., 1962; KAUL, 1964; GRILLMAIER, 1964; HURSH, 1965).

Discussion of the results

Dose rate calculations in patients with long-term Thorotrast burdens presume knowledge of organ distribution of Th^{232} and activity ratios between Th^{232} and its daughters. For that purpose data of others and those of own investigations were compiled from literature as basis for calculating present "best estimates". All data only refer to the less complicated case of purely intravascular injection of Thorotrast, and may not be applied without precautions to cases of retrograde Thorotrast pyelography, or patients with important perivascular Thorotrast deposits.

Considerable caution is also called when using the results of the average Th^{232} organ distribution to predict whole body and organ Thorotrast burden from tissue analyses of any one Thorotrast patient, or to estimate individual organ distribution of Th^{232} and its daughters from results of whole-body counting. To the same extent all calculated steady state activity ratios as given above may only be considered as coefficients for dose rate estimates in typical cases of long-term Thorotrast burdens.

The limited relevance of these data, though nevertheless to be necessary at least for estimating mean organ doses, and unlikely to undergo major revision in future, is mainly due to the fact, that in most cases results of tissue samples had to

be extrapolated to whole organs, and different pathological conditions from which these patients suffered were not able to be considered with regard to distribution of Th^{232} and daughters within the organism.

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TABLE 3 ESTIMATED ORGAN DISTRIBUTION OF Tb^{232} IN THYROID PATIENTS AS % OF INJECTED Tb^{232}

AUTHOR	LIVER	SPLEEN	RED BONE MARROW	MARROW-FREE SKELETON	LUNG	KIDNEY
REYNOLDS ¹ 1957	77	16.8	3.44	—	—	—
SAUL ² 1964, 1968a 1968b	62	17	6.38	1.6	0.85	—
TEUKAMOTO ³ 1966	56.8	12.4	—	—	—	—
PARKE ⁴ et al. 1969	75	13.6	0.3	21	0.3	0.3
LUCAS ⁵ et al. 1962	—	8.6	—	—	—	—
GOLDIN ⁶ et al. 1972	237	16.7	484	262	—	—
SAUL ⁷ (This paper)	89	26.6	0.3	39	0.7	0.7

¹ INTRAVASCULAR INJECTION OF THYROID

² CALCULATED FROM RESULTS OF WHOLE-BODY COUNTING

(AVERAGE VALUES OF 8 PATIENTS)

³ CALCULATED FROM RESULTS OF TISSUE ANALYSES AND/OR WHOLE BODY COUNTING AND REFERRED TO ORGAN MASSES OF STANDARD MAN

⁴ OWN CALCULATION FROM THE AUTHOR'S RESULTS OF WHOLE BODY COUNTING AND KNOWN AMOUNTS OF INJECTED THYROID-TRAST TO PATIENTS; ACTIVITY RATIO TO Tb^{232} / Tb^{232} ASSUMED TO BE 0.39 (AVERAGE VALUES OF 8 PATIENTS)

⁵ CALCULATED BY THE AUTHOR FOR THE STANDARD MAN (8 PATIENTS)

⁶ OWN CALCULATION FROM THE AUTHOR'S RESULTS OF TISSUE ANALYSES AND KNOWN AMOUNT OF INJECTED THYROID-TRAST TO PATIENT (FOUR)

⁷ PRESENT "BEST ESTIMATES" CALCULATED FROM PUBLISHED DATA AND REFERRED TO STANDARD MAN

TABLE 4 STEADY-STATE ACTIVITY RATIOS IN LIVER OF MAN

AUTHOR	TIME OF THYROID BLIND	Pb^{214}/Th^{232}	Th^{232}/Th^{232}	Pb^{214}/Th^{232}	Pb^{214}/Pb^{214}	Pb^{214}/Pb^{214}
ALPERT ¹ 1958	13.5 y	0.88	0.80	0.88	0.38	—
	14.5 y	0.86	0.72	0.87	0.45	—
HILLER ² et al. 1958	9 d	0.96	0.78	—	—	—
BASENGA ³ et al. 1960	15 y	0.61	0.88	—	—	—
KALIA ⁴ et al. 1965, 1969	LONG-TERM (?)	—	0.80	—	—	—
	—	0.40	0.87	—	—	—
	—	0.40	0.82	—	—	—
	—	0.40	—	—	—	—
GOLDIN ⁵ et al. 1972	LONG-TERM (?)	0.30	0.84	0.87	0.53	—
PARKE ⁶ et al. 1969	49 d	0.30	—	0.59	—	—
	49 d	0.22	1.01	0.85	—	—
	26 d	0.20	0.88	0.83	—	—
	49 d	0.19	0.88	0.59	0.62	—
	11 y	0.38	1.00	—	—	—
	26 y	0.4	1.01	0.75	—	—
WROEMER ⁷ et al. 1971	22 - 30 y (NO SAMPLES)	—	0.83	—	—	—
GOLDIN ⁸ et al. 1972	19 y	0.32	0.87	0.76	11.26	—
	19 y	0.26	0.85	0.75	0.74	—
AVERAGE		0.38	0.80	0.80	0.55	—

() UNCONSIDERED VALUE

TABLE 5. STEADY STATE ACTIVITY RATIOS IN SPLEEN OF MAN

AUTHOR	TIME OF INTERVIEW	1975/1974	1976/1975	1977/1976	1978/1977	1979/1978
RAJESH et al, 1980	12 y	0.74	0.61	0.74	0.17	-
MURPHY 1982	20 y	0.63	0.48	-	-	-
KALIA et al, 1983	LONG-TERM(1)	0.71	0.60	0.50	0.48	-
	-	0.30	0.05	0.00	0.00	-
	-	17.00	0.05	-	-	-
	-	-	0.00	0.01	0.40	0.27
GOLDIN et al, 1983	LONG-TERM(1)	0.34	0.04	-	-	-
	-	0.20	0.05	0.01	0.17	-
PAAR et al, 1983	4.0 d	0.30	-	0.74	-	-
	4.0 d	0.30	0.07	0.74	-	-
	20 d	0.20	0.07	0.63	-	-
	4.0 d	0.21	0.04	0.04	0.42	-
	11 y	0.26	0.07	-	-	-
	20 y	0.04	1.00	0.74	-	-
WESCHER et al, 1981	20-30 y	-	0.07	-	-	-
	R. SAMPLE(1)	-	-	-	-	-
GOLDIN et al, 1983	10 y	0.30	0.07	0.07	0.44	-
	10 y	0.20	0.00	0.05	0.30	-
LUCAS et al, 1982	20 y	0.35	0.07	0.77	0.00	1.10
AVERAGE		0.37	0.05	0.00	0.40	0.52

(1) UNCONSIDERED VALUE

TABLE 6. STEADY STATE ACTIVITY RATIOS IN BONE MARROW AND BONE'S CONTAINING MARROW OF MAN

AUTHOR	TIME OF INTERVIEW	TISSUE SAMPLE	1975/1974	1976/1975	1977/1976	1978/1977	1979/1978
MURRAY 1982	15-20y	BODY OF VERTEBRA	-	1.0	-	-	-
	20y	HEAD OF FEMUR	-	0.0	-	-	-
	20y	STERNUM BONE	0.2	0.0	-	-	-
RAJESH et al, 1980	-	STERNUM BONE	-	0.7	-	-	-
	-	RIB	0.0	0.00	-	-	-
FURNER et al, 1980	-	RIB	-	0.02	-	-	-
	30y	STERNUM	0.0	0.17	-	-	-
	15-20y	BODY OF VERTEBRA	-	0.0	-	-	-
KALIA et al, 1983	-	HEAD OF FEMUR	-	0.0	-	-	-
	10y	RIB	0.24	0.00	-	-	-
KALIA et al, 1983	LONG-TERM(1)	BONE MARROW	0.10	1.1	-	-	-
	LONG-TERM(1)	BONE MARROW	0.31	0.0	-	-	-
	LONG-TERM(1)	BONE MARROW	0.31	0.0	-	-	-
PAAR et al, 1983	4.0d	RIB	0.0	0.4	-	-	-
	4.0d	VERTEBRA	0.0	0.0	-	-	-
	4.0d	RIB	0.00	0.0	0.0	-	-
	11y	VERTEBRA	1.2	0.0	0.0	-	-
	11y	RIB	0.02	0.0	-	-	-
	4.0d	VERTEBRA	0.03	0.0	-	-	-
20y	4.0d	RED BONE MARROW	0.01	0.00	0.00	1.1	-
	20y	RED BONE MARROW	-	1.0	0.50	-	-
	20y	BONE MARROW	-	-	-	-	-
GOLDIN et al, 1983	10y	BONE MARROW	-	-	0.00	0.00	-
	10y	BONE MARROW	0.27	0.00	0.24	0.00	-
AVERAGE			0.61	0.10	0.0	0.20	-

TABLE 10
PRESENT "BEST ESTIMATES" OF STEADY STATE ACTIVITY RATIOS
IN PATIENTS WITH LONG-TERM THOROTRAST BURDEN^{a)}

ORGAN	$R_{\text{L}}^{228}/Tl^{232}$	$Tl^{232}/R_{\text{L}}^{228}$	$R_{\text{S}}^{228}/Tl^{232}$	$Pb^{210}/R_{\text{L}}^{228}$	Bq^{210}/Pb^{210}
LIVER	0,4	0,9	0,7	0,6	(0,7)
SPLEEN	0,4	0,9	0,8	0,4	0,7
RED BONE MARROW	0,4	1,0	0,9	1,0	(1)
MARROW-FREE BONE	1,2	1,1	1,5	1,0	(1)
LUNG	0,5	0,9	~1,5	~1,0	(1)
KIDNEY	~0,2	1,5	~1	~1	(1)

^{a)} INTRAVASCULAR INJECTION OF THOROTRAST

() ASSUMED VALUES IN ABSENCE OF RESULTS
 OF ACTUAL MEASUREMENTS IN THOROTRAST PATIENTS

TABLE 11 **STEADY STATE ACTIVITY RATIOS IN DIFFERENT ORGANS OF ANIMALS COMPARED TO THOSE**
IN THE "STANDARD THOROTRAST PATIENT"
(LONG-TERM BURDEN OF INTRAVASCULARLY INJECTED THOROTRAST)

AUTHOR	ANIMAL / MAN	ORGAN	$R_{\text{L}}^{228}/Tl^{232}$	$Tl^{232}/R_{\text{L}}^{228}$	$R_{\text{S}}^{228}/Tl^{232}$	$Pb^{210}/R_{\text{L}}^{228}$	Bq^{210}/Pb^{210}
PARKS ^{et al.} 1967	8 RATS (20-800 d) 1000 (21 d)	LIVER	0,28	0,87	0,48	0,46	0,75
		SPLEEN	0,23	0,7	0,38	0,38	0,76
		RED BONE MARROW	-	-	-	-	-
MEYER ^{et al.} 1968 KALL, 1969	24 RABBITS (10-531 d)	LIVER	0,35	0,88	0,75	0,28	1,9
		SPLEEN	0,38	0,85	0,68	0,23	2,8
		RED BONE MARROW	0,38	0,85	0,64	0,87	-
KALL (this paper)	"STANDARD THOROTRAST PATIENT"	LIVER	0,4	0,9	0,7	0,8	1,07
		SPLEEN	0,4	0,9	0,8	0,4	0,7
		RED BONE MARROW	0,4	1,0	0,9	1,0	(1)

() ASSUMED VALUES IN ABSENCE OF RESULTS OF ACTUAL MEASUREMENTS IN THOROTRAST PATIENTS

^{a)} AVERAGE VALUES CALCULATED FROM THE AUTHORS' SPECIFIED DATA

**TABLE PRESENT "BEST ESTIMATES" OF STEADY STATE ACTIVITY
 12 RATIOS (NORMALIZED TO UNITY FOR Th^{232}) IN WHOLE
 BODY OF PATIENTS WITH LONG-TERM THOROTRAST
 BURDEN ^{a)}**

RADIONUCLIDE	FROM TISSUE ANALYSES (WEIGHTED MEANS ^{a)})	CALCULATED FROM EXCRETION ANALYSES ACCORDING TO	
		KAUL, 1965 ^b	PARR <i>et al</i> , 1969
$\text{Th}^{232} / \text{Th}^{232}$	1,00	1,00	1,00
$\text{Ra}^{226} / \text{Th}^{232}$	0,43	0,52	0,5
$\text{Th}^{230} / \text{Th}^{232}$	0,40	0,48	0,46 - 0,5
$\text{Ra}^{226} / \text{Th}^{232}$	0,34	0,44	0,47 - 0,48
$\text{Po}^{210} / \text{Th}^{232}$	0,32	0,4	0,37 - 0,44
$\text{Bi}^{210} / \text{Th}^{232}$	0,28	-	-

^{a)} INTRAVASCULAR INJECTION OF THOROTRAST

^{b)} WEIGHTING FACTORS ACCORDING TO ORGAN
 DISTRIBUTION OF Th^{232} (SEE TABLE 2)

Radiation Dose in Lungs

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Abstract

The fundamentals for calculating radiation doses in the different parts of the lungs of thorotrast patients are described and doses and dose-rates depending on time after injection of the contrast medium and on the injected amount are given.


Key words: Thorotrast
Thoron
Lung-burden

The calculations of the radiation doses in the different regions of the lungs of Thorotrast patients are based on the following fundamentals (Grillmaier and Muth).¹⁾:

1. On the results of measurements of the thoron concentration in the exhaled air. Measurements of the first 46 patients at the beginning of the Thorotrast research program had shown that in good agreement with other series of investigations (Rundo)²⁾ patients with only RES-deposits (without paravascular infiltrates) on the average exhale $(8 \pm 3) \%$ of thoron. More recent measurements of thoron concentration in the exhaled air of further 61 patients have confirmed this value again.
2. The geometrical data as length, diameter, volume, and number of the different parts of the bronchial tree and alveoli, which are necessary for the calculations, we have taken from the anatomic lung model of Landahl.⁴⁾ This model is shown in table 1. It also includes the ciliary transport velocities.

Table 1

Anatomic model of human lung



Region	Number	Diameter (cm)	Length (cm)	Total surface area (cm ²)	Total volume (cm ³)	Ciliary transport velocity (cm/min)
Trachea	1	1.6	12	60	24	15
Main Br.	2	1.0	6	40	10	0.8
Lobar Br.	12	0.4	3	45	5	0.3
Segm Br.	100	0.2	15	100	5	0.1
Subseg Br.	800	0.15	0.5	200	10	0.02
Terminal Br.	6×10^4	0.06	0.3	3400	50	0.004
Resp. Br.	2×10^5	0.05	0.15	4700	60	—
Alveol. duct.	5×10^6	0.04	0.05	30,000	300	—
Alveol. sac.	5×10^7		0.04	250,000	2500	—

3. For the calculations the following physiological mean values are assumed:

- a) Breathing rate is taken as 7 l/min. This value is in agreement with the mean value we have found for thorotrast patients.
 - b) The breathing volume is taken as 0.5 l.
 - c) The volume of the lungs is taken as 3.25 l.
 - d) The total mass of the respiratory zone (resp.br., alveol.duct., alveol.sacc.) is taken as 800 g. Density of lung mass is 1 g/cm^3 .
4. The penetration depth of the α -particles is assumed to be about 50 μ . From this value and unit density the mass of the irradiated lung tissue in the bronchial tree (excluding the resp. zone) is calculated.
5. Only the α -particle radiation doses as the most important factor are calculated.

For computing the radiation dose at a certain time after injection the time dependend behaviour of the dose rate has to be known. The dose rate however is depending on the activity ratios of the thorium-232 daughters in the organism.

The following assumptions confirmed by special investigations have been made:

- a) At the time of injection the thorotrast does not contain radium 228 (Rundo,³) Kaul,⁴) Rotblat and Ward,⁵) but the equilibrium amount of thorium 228 (Kaul,⁴) Parr⁶).
- b) After injection 50 % of the radium 228 which grows in vivo from thorium 232 is excreted. It is assumed that no appreciable amounts of other daughters are excreted. From these assumptions the time dependence of the thoron production is evaluated.

To receive the dose rates or doses the knowledge of the activity ratios of thoron and its daughters in the lungs and on the lung epithelium is also necessary. For investi-

gating these activity ratios the following factors are taken into a account:

- a) The deposition of thoron daughters built ^{up} in the breathing air on the lung epithelium.
- b) The attachment of thoron daughters to aerosol particles in the air which possibly leads to a decrease in the deposition on the lung tissue.
- c) The transfer for thoron daughter particles deposited on the mucus layer of the lung epithelium or still in the air out of the lungs.

The results of the computations establish that in the respirative zone practically all polonium-216 and lead-212 atoms are deposited on the walls of the respirative bronchi and alveoli before decaying ore before attachment to aerosol particles is possible. It was assumed, that the particles remain at the site of deposition so that in the respirative zone radioactive equilibrium between thoron, polonium-216, lead-212 and the other thoron daughters exist.

In the bronchial tree including the bronchi up to the trachea the mean residence time of the air in comparison to the half life of polonium-216 is so long, that the radioactive equilibrium between thoron and polonium-216 practically exists at once, whereas the half life of lead-212 is much too long so that no lead-212 activity can grow up in the air. In addition to these facts it was established, that even in the case of complete deposition of polonium-216 on the mucus layer of the epithelium and even in the region of the highest ciliary transport velocity the radioactive equilibrium between thoron and polonium-216 is not disturbed.

In comparison even in the region of lowest velocity of ciliary transport no appreciable amount of lead-212 activity is built up by decay of deposited polonium-216.

Therefore the computations of the radiation doses in the different parts of the bronchial tree concerning the activity

ratios of thoron and its daughters are based on the following assumptions:

During exhalation air with thoron but free of polonium-216 and lead-212 is introduced from the alveolar region in the upper airways. Within a very short time polonium-216 is in radioactive equilibrium with thoron independent of the fact, that it may be deposited on the mucus layer or not.

Lead-212 however cannot build up an appreciable amount of activity neither in the air nor on the epithelium.

During the inhalation period and the period of air retention in the lungs the thoron containing air is drawn into the respirative zone. The bronchial tree is filled with fresh thoron free air.

Polonium-216 particles which perhaps are deposited on the epithelium decay at once. No irradiation occurs during this period. Only in the terminal bronchi it is assumed, that the inhaled air is mixed uniformly with the thoron containing air of the respirative zone.

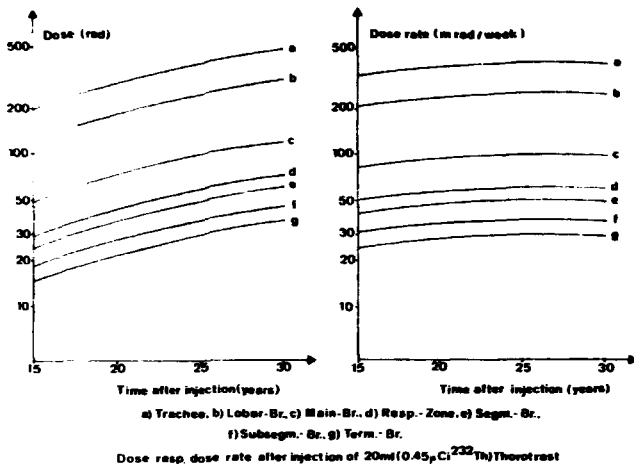
The time dependent relationship of the dose-rates and doses in the different parts of the lungs during the period of 15 to 30 years after injection of 20 ml thorotrast is shown in figure 1.

The increase of the dose rates is caused by the increase of the radium-228 activity which grows up in vivo.

Table 2 contains the alpha-ray doses 30 years after the injection of different amounts of thorotrast in the different parts of the lungs. It can be seen, that the doses vary markedly in the different regions. If one takes into consideration the biological effectiveness of alpha-rays the equivalent doses exceed the maximum permissible doses partially by a high factor.

It must be mentioned that the absorption of alpha-ray energies in the air and in the mucus layer have not been taken

Figure 1



into account. Therefore the radiation doses in the upper airways especially in the trachea are a little too high. The real values may be 20 to 30 % lower.

A further comment is to make: Many of the patients we have evaluated have additional large paravascular infiltrates filled with thorotrast. As recent measurements have established, practically no thoron is released out of these infiltrates. But because these patients have in a first approximation an equal amount of thorotrast in the organs of the RES, for calculating the lung doses we take an exhalation rate of $(4 \pm 1) \%$ relating to the whole body burden measured. This is a mean value we have obtained by measuring thorotrast patients with both, RES-deposits and paravascular infiltrates.

Table 2

INJECTED THOROTRAST (ML) :	5	12	20	45
RESP. ZONE	18	44	73	165
TERM. BR.	9	22	36	82
SUBSEGM. BR.	11	27	45	102
SEGM. BR.	15	36	60	136
LOBAR BR.	30	73	122	274
MAIN BR.	77	184	306	689
TRACHEA	122	293	488	1100

DOSE (RAD)

Concluding the considerations one has to take into account the possibility of additional irradiations of the lungs by primary thorotrast depositions in this organ or respectively in the lymph nodes placed in the lungs.

Table 3 contains the results of investigations concerning this point. The mean thorotrast content in lung tissue is 0.7 % of the whole body burden. This amount would cause a alpha-ray dose rate of 3 % in the trachea to 33 % in the terminal bronchi of that applicated by thoron and its daughters in these parts of the lungs 30 years after injection of thorotrast. Calculating the dose rate by primary thorotrast deposits in the lungs a uniform distribution of ThO_2 was assumed.

Table 3

RADIATION DOSE DISTRIBUTION IN LUNGS OF THOROTRAST PATIENTS

Table 2. ^{232}Th -content of lungs (Whole organ relative to whole body burden)

Author	Number of cases	Duration of body burden	^{232}Th -content (%)	
HURSH <i>et al</i>	4	17 days-19 yr	1.4	1.4×4
KAUL	1	long term	0.05*	0.05×1
DUDLEY	1	~25 yr	0.14*	0.14×1
PARR	5	26 days-26 yr	0.3	0.3×5
Sum	11			7.29
Average				$7.29:11 = 0.66\%$

* Calculated from measured ^{232}Th -content, assuming that the activity ratios of ^{232}Th and its followers in the lung are the same as in the organs of the RES.

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Mean Organ Dose Rates in Man following
intravascular Injection of Thorotrast*

by

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Abstract

Estimates of mean organ dose rates for patients with long-term burdens of intravascularly injected Thorotrast (10, 30 and 50 ml) were performed based upon present "best estimates" on tissue distribution and steady state activity ratios of Th^{232} and daughters. Self-absorption of emitted radiation due to aggregation of the ThO_2 particles within the living tissues was considered by application of conventional methods of empirical origin. In addition, long-term (0,125-392 days) animal experiments were done with rabbits, considering the size of the ThO_2 aggregates in vivo, and their variation with time in tissues of the reticuloendothelial system, by analyses of histological sections using a picture analyzing computer ("flying spot analysis").

* Dedicated with Gratitude to Prof. Dr. B. Rajewsky on his 80th Birthday.

For an intravascular injection of 50 ml Thorotrast the mean α -ray dose rate in the liver, spleen, and bone marrow proved to be about 40, 120 and 23 rd/year, respectively. The corresponding self-absorption correction factors for α -particles yielded 0,52, 0,29 and 0,87, respectively, if calculated according to conventional methods. By computerized picture analyses of rabbit tissue samples (liver and spleen) containing Th^{232} at comparable concentrations self-absorption correction factors have been calculated which proved to be approximately 0,6 and 0,45, respectively.

Moreover, the results of the animal experiments have indicated the process of aggregation of ThO_2 particles within the liver tissue to be continuing for times of more than 400 days after Thorotrast injection. In the spleen, however, the aggregates size distribution remained nearly constant at times of more than about 150 days after Thorotrast application.

Introduction

Thorotrast dosimetry is a problem of great complexity due to incomplete knowledge of purely physical, physicochemical, and biological factors, affecting radiation dose to organs of Thorotrast patients. Nevertheless, as Thorotrast patients possibly constitute an important and unique population for the study of low-level and long-term irradiation effects in man, calculations of mean dose rates delivered to the tissues of Thorotrast patients need to be done. For that reason according to previous investigators (RUNDO, 1958; 1960; HURSH et al., 1957; HURSH, 1965; KAUL, 1964; 1965a,b,c; MARINELLI, 1965; DUDLEY, 1966; PARR et al., 1969) the present study is concerned with the evaluation of dose rates, as to derive the current "best estimates" based on average data on organ distribution of Th^{232} , and on steady state activity ratios between Th^{232} and its daughters, as had been compiled on the occasion of the present meeting (KAUL, 1973).

In addition, self-absorption of emitted radiation due to aggregation of colloidal thorium dioxide in tissues of the RES will be dealt quantitatively based on recent results of animal experiments with rabbits.

Results

1 Calculation of mean dose rates

As a presupposition for dose rate calculations, the average organ distribution of Th^{232} has been calculated as present "best estimate" applied to a "standard Thorotrast patient" after intravascular injection of Thorotrast (KAUL, 1973). The results once more summarized in table 1, indicate an average fractional retention of Th^{232} in the liver and spleen of 60 and 26 %, respectively. The corresponding value for the red bone marrow proved to be about 9 %, that for the total skeleton was less than 4 %. Within the lungs and kidneys less than 1 % of whole body Th^{232} were estimated to be retained.

As even in long-term cases of Thorotrast burdens thorium daughters will never reach radioactive equilibrium with Th^{232} due to continuous translocation within the body and excretion from the body, dose rate calculations presuppose additional information on the steady state activity ratios between Th^{232} and its radioactive decay products. The corresponding data have been derived for various tissues of human Thorotrast cases from published equilibrium activity ratios between the different Th^{232} daughters, and (normalized to unity for Th^{232}) presented as current "best estimates" in table 2.

From the purely physical point of view these data, completed by data on radiation type and average energy per disintegration of each radionuclide, are sufficient for dose rate calculations. However, from the early investigations by BERENBAUM et al. (1953) colloidal ThO_2 proved to be deposited within the living tissues in aggregates or granules up to $100\text{ }\mu\text{m}$ across, giving rise to substantial self-absorption of α -particles. By combination of autoradiography and light microscopy ROTBLAD et al. (1953) were able to estimate the fraction F of α -ray energy being dissipated outside the ThO_2 aggregates, from observed track concentrations and lengths in the nuclear track emulsions. Further investigations by WARD (1955), GUIMARAES et al. (1956), and RUNDO (1958) yielded the degree of self-absorption to be dependent on the concentration of Th^{232} in the tissue, and on the period of deposition.

According to the results of these authors, the average fraction F of the α -ray energy being dissipated outside the

TABLE 1

PRESENT "BEST ESTIMATES" OF ORGAN DISTRIBUTION
OF Th^{232} IN A STANDARD THOROTRAST PATIENT^{a)}

ORGAN	ORGAN WEIGHT IN STAND. MAN W (Kg)	Th^{232} CONC. IN ORGAN (C), REL. TO LIVER	C/W	ORGAN DIST. OF Th^{232} IN STAND. PAT (%)
LIVER	1.7	100	170.0	59
SPLEEN	0.15	506	75.9	26.5
RED BONE MARROW	1.5	178	26.7	9.3
MARROW-FREE SKELETON	7.0	1.6	11.2	3.9
LUNG	1.0	1.96	1.96	0.7
KIDNEY	0.3	1.33	0.4	0.7

a) INTRAVASCULAR INJECTION OF THOROTRAST

TABLE 2

PRESENT "BEST ESTIMATES" OF STEADY STATE ACTIVITY RATIOS (NORMALIZED TO UNITY FOR Th^{232})
IN DIFFERENT ORGANS OF PATIENTS WITH LONG-TERM THOROTRAST BURDEN^{a)}

ORGAN	$\text{Th}^{232} / \text{Th}^{232}$	$\text{Ra}^{226} / \text{Th}^{232}$	$\text{Th}^{230} / \text{Th}^{232}$	$\text{Ra}^{224} / \text{Th}^{232}$	$\text{Ra}^{226} / \text{Th}^{232}$ + $\text{Pa}^{227} / \text{Th}^{232}$	$\text{Po}^{210} / \text{Th}^{232}$	$\text{Bi}^{210} / \text{Th}^{232}$
LIVER	1	0.4	0.36	0.26	0.20	0.15	0.17
SPLEEN	1	0.4	0.36	0.29	0.23	0.17	0.08
RED BONE MARROW	1	0.4	0.40	0.36	0.72	0.36	0.36
MARROW-FREE SKELET.	1	1.2	1.32	1.80	1.80	1.80	1.80
LUNG	1	0.8	0.43	0.68	0.76	0.76	0.76
KIDNEY	1	0.7	0.7	0.7	0.34	0.3	0.7

a) INTRAVASCULAR INJECTION OF THOROTRAST

ThO_2 aggregates in tissues of long-term Thorotrast body burdens can be represented empirically as a function of mean Th^{232} tissue concentration as follows:

$$F = 0,645 \exp(-1,50A) + 0,355 \exp(-0,047A)$$

where A is the concentration of Th^{232} expressed as dpm/mm^3 .

Based upon this conventional concept of calculating self-absorption, and considering both the above mentioned organ distribution of Th^{232} and equilibrium activity ratios mean organ α -dose rates D' (rd/year) have been estimated for 10, 30 and 50 ml Thorotrast intravascularly injected 20-25 years previously. The results of the estimations are summarized in table 3 together with the corresponding self-absorption correction factors for α -particles. For example in case of 50 ml Thorotrast application the mean α -ray dose rate for the liver is only about 50 % of that if self-absorption by aggregation of ThO_2 were not to be considered. Due to the high Th^{232} concentration of the spleen which proved to be approximately 500 % of that of the liver (KAUL, 1973), self-absorption amounts to 70 % so that the mean α -ray dose rate of the spleen is only 3 times that of the liver. According to the less concentration of Th^{232} in other tissues, self-absorption of α -particle energy is only 13 % in red bone marrow and may be neglected for marrow-free skeleton, lungs and kidneys.

During the past, some others have also estimated dose rates to different organs of Thorotrast patients which were, in part, normalized to an injected amount of 50 ml Thorotrast for reasons of comparison as has been done previously by PARR et al. in 1969. The results are contained in table 4 and prove to be in rather good agreement with the above "best estimates". This is partly due to the fact that the present authors' calculations have also relied on data of previous publications in this field. It should be pointed out, however, that some data which had to be normalized to 50 ml Thorotrast had been calculated on the assumption of proportionality between dose rates and volume of administered Thorotrast, neglecting differences in self-absorption of radiation. Dose rates to the lungs have to be regarded only as rough estimates as they do not take into account differences in the various regions of the lungs as has been recently shown by GRILLMATER et al (1971). Moreover it

TABLE 3
MEAN α -RAY DOSE RATES IN DIFFERENT ORGANS OF A STANDARD PATIENT AFTER
INTRAVASCULAR INJECTION OF 10, 30 AND 50 ml THOROTRAST (LONG-TERM THORO-
TRAST BURDEN)

ORGAN	$V=10\text{ml}$			$V=30\text{ml}$			$V=50\text{ml}$		
	A (Th^{232}) (nCi)	\bar{F}	D_0 (rd/y)	A (Th^{232}) (nCi)	\bar{F}	D_0 (rd/y)	A (Th^{232}) (nCi)	\bar{F}	D_0 (rd/y)
LIVER	28	0.85	13	293	0.65	30	655	0.52	41
SPLEEN	58	0.51	4.2	176	0.33	8.2	294	0.29	120
RED BONE MARROW	21	0.57	5.2	82	0.52	14.0	100	0.67	233
MARROW-FREE SKELETON	0.7	1	15	26	1	44	433	1	23
LUNG	155	1	5.7	466	1	12.0	277	1	203
KIDNEY	0.22	1	0.18	0.67	1	0.53	1.1	1	0.88

\bar{F} : SELF ABSORPTION CORRECTION FACTOR

TABLE 4: ESTIMATED α -RAY DOSE RATES TO ORGANS OF
PATIENTS WITH LONG-TERM THOROTRAST BURDENS
(INTRAVASCULAR INJECTION OF 50 ml THOROTRAST)

AUTHOR	α -RAY DOSE RATES (rd/y) IN DIFFERENT ORGANS				
	LIVER	SPLEEN	RED BONE MARROW	MARROW-FREE SKELETON	LUNG
MURSH et al., 1957	70	70	7	—	25 ¹
MUNDG, 1960	68	170	10-61	—	5 ²
MUNDG, 1960	54	30	10	30-95	4, 3 ³
KALLIC ⁴ , 1964, 1965 a, b, c	86	145	30	2	—
MANNHELL, 1965	117 ^{3B}	103 ^{3B}	230 ^{3B}	31	12.6
DUDLEY ⁴ , 1966	62	81	16	2	1.8
FAHRY ⁵ , et al., 1969	71	100	19	2	12
GOLDH et al., 1972	32	202	4.7	12.2	—
	83	173	4.7	12.2	—
KALLIC ⁴ et al. (this paper)	41	130	23.2	7.3	24.2

¹ DOSE RATE DUE TO Th^{232} AND DAUGHTERS ACTUALLY DISTRIBUTED IN ORGAN

² EXPOSED Ra^{226} LUNG DOSE RATE

³ SELF-ABSORPTION OF α -PARTICLES WITHIN Th^{232} APPROXIMATES
NEGLECTED

should be pointed out, that for the purpose of the present dose estimates only α -ray dose rates are considered as the β - and γ -ray dose rates are comparably low (less than 10 %).

2 Estimation of self-absorption

It follows from what has already been said that radiation doses in tissues of Thorotrast patients are reduced to a considerable extent by self-absorption of radiation emitted from ThO_2 aggregates. The magnitude of this effect and the variation of self-absorption with time of Thorotrast tissue burden are not well established. For the concept of estimating the average fraction for the α -ray energy being dissipated outside the ThO_2 aggregates in tissue is based upon autoradiography, and does not take account of the wash-out of the short-lived thorium daughters in vivo.

For that reason animal experiments were done in rabbits considering the size and variation with time of ThO_2 aggregates in organs of the RES. Each animal was injected in the ear vein with 2 ml of Thorotrast supplied by Testagar Fellows (Detroit, Mich., USA), corresponding to an average injected amount of 50 ml in man. The time of Thorotrast burden varied between 0,125 and 530 days.

At different times after administration of Thorotrast animals were sacrificed, and dark-field microphotographies of unstained histological sections of the liver and spleen were made (see fig. 1). The films were evaluated for particle size distribution of ThO_2 aggregates using a picture analyzing computer ("flying spot analysis"). By this method as described earlier by ABMAYR et al. (1970) and HINDRINGER et al. (1972) sections of the pictures, each of $0,462 \text{ mm}^2$ area (corresponding to 240×240 bits), were stored on-line with a local resolution of 1 bit (corresponding to $8,2 \mu\text{m}^2$) and evaluated by the computer.

Considering both the measured equilibrium activity ratios between Th^{232} and its daughters in tissue samples of the liver and spleen, and the ranges of the emitted α -particles in ThO_2 , the fraction N_α^-/N_α of α -particles emitted from ThO_2 aggregates were calculated as function of the area of cross sections of ThO_2 aggregates, having been assumed to be of spherical shape. The results of these estimates are presented in figure 2 for steady



Fig. 1: Dark-field microphotographies of spleen tissue sections 1 day (left) and 392 days after intravascular injection of 2 ml Therotrast into a rabbit (Magnification factor about 120)

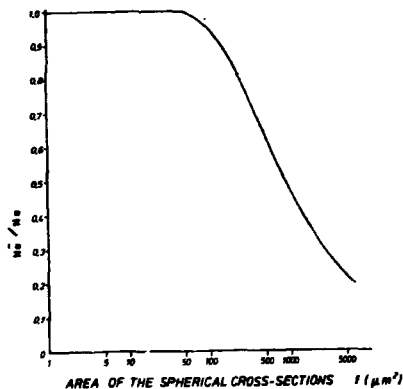


Fig. 2: Fraction $N_{\alpha}^{-} / N_{\alpha}$ of α -particles emitted from ThO_2 aggregates as function of the area of spherical cross sections

state conditions, indicating 100 % emission of α -particles from spherical ThO_2 aggregates up to cross sections of about $50/\mu\text{m}^2$ area.

From these results corresponding area classes were calculated for decreasing α -particles emission probabilities in steps of 5 % between 1 and 0,2, in order to classify by computer the number of ThO_2 aggregates of each tissue section for different times of Thorotrast burden. As an example, results are shown in figure 3 for tissue samples of the liver and spleen 1 and 392 days after intravascular injection of Thorotrast into rabbits. According to these results about 90 % of ThO_2 aggregates of the spleen had diameters between 4 and $17/\mu\text{m}$ 1 day after Thorotrast application, while 392 days thereafter the corresponding fraction had decreased to about 50 %. At that time the maximum particle diameter proved to be $70/\mu\text{m}$ compared to the liver for which maximum particle diameters of $37/\mu\text{m}$ were observed.

As the average rate of α -particles created by decay of Th^{232} and its α -instable daughter products is proportional to the mean volumes of ThO_2 aggregates in the tissues, the fraction of α -particles emitted from the aggregates had been possible to calculate from the actual ThO_2 particles size distribution for various times of Thorotrast burden. In figure 4 the results of these investigations are shown for the liver and spleen, indicating the process of aggregation of ThO_2 particles within liver tissue to be continuing for times of more than 400 days after Thorotrast application. In the spleen, however, the aggregates size distribution remained nearly constant at times of more than about 150 days after Thorotrast injection. The corresponding self-absorption correction factors for the liver and spleen expressed by the numbers of α -particles emitted from ThO_2 aggregates (N_{α}^-) related to those created by decay of Th^{232} and its α -instable daughters (N_{α}^+) proved to be about 0,65 and 0,45, respectively, for a 50 ml equivalent Thorotrast burden of 400 days.

Though the presented results did not yet take into account the energy spectrum of the α -particles being emitted from ThO_2 aggregates, the actual fraction of the α -ray energy being dissipated outside the aggregates should not be too different from

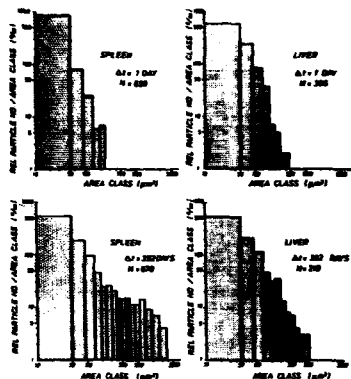


Fig.3: Relative number of the ThO₂ aggregates as function of area class in tissue samples of liver and spleen for Thorotrast burdens of 1 and 392 days

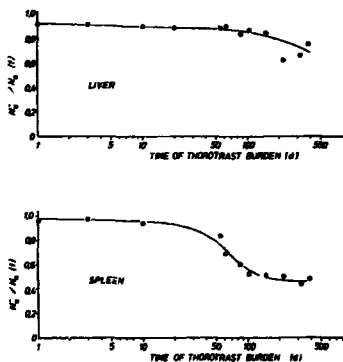


Fig.4: Fraction of α -particles emitted from ThO₂ aggregates as function of time of Thorotrast burden

the above estimates if one considers the very simplified assumptions on both the shape and the correlation between volume and microscopically determined area of the aggregates. Finally we can conclude from the agreement of the data on self-absorption estimated according to the conventional concept and those obtained by computerized picture analyses of animal tissue samples (0,56:0,65 for the liver; 0,35:0,45 for the spleen) that the prevailing method of calculating the amount of dose rate reduction is quite sufficient for the purpose of Thorotrast dosimetry.

Discussion of the results

Dose rate calculations have been done for long-term Thorotrast burdens after injection of 10-50 ml colloidal thorium-dioxide to patients. As the presented data only refer to the less complicated case of purely intravascular injection of Thorotrast the results may not be applied without precautions to cases of retrograde Thorotrast pyelography, or patients with important perivascular Thorotrast deposits at the site of former injection.

Moreover the published data are to be considered as current "best estimates" of mean tissue dose rates as they are based upon average tissue distribution of Th^{232} and steady state activity ratios between Th^{232} and its daughters which can be submitted to wide variations from patient to patient. In addition, the calculations did not allow for the hitherto quantitatively unknown process of continual redistribution of Thorotrast aggregates within the organs of the RES, as well as for inhomogeneities in micro-distribution of thorium aggregates which can give rise to local dose rates up to at least one order of magnitude.

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Assessment of Organ Distribution of Thorium
by Neutron-Activation-Analysis

by

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Abstract

The thorium content of 2500 specimens was determined by means of neutron activation analysis. The samples were taken out of the different regions of the body from 17 Thorotrast-patients after death. The highest concentrations were found in the main organs of the RES (up to 90 mg Th/g). The least concentration was found in the brain (0.05 µg/g). The variations of thorium within the organs were remarkable. In the liver of one and the same patient the variation could be up to a factor of 50, in the bone marrow up to 100 and in the lymphatic nodes up to 1000.

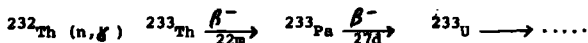
Introduction

In the last three years we had the opportunity to study, in detail, specimens taken from 17 different Thorotrast-patients after death. There were three women and 14 men who were between 46 and 72 years old. They had received Thorotrast in unknown amounts 25 to 32 years before they died.

In total we investigated 2500 samples out of the different regions of the body. The samples were examined by histology and autoradiography. Furthermore the content of thorium was determined quantitatively. I will speak about the quantitative results. Mr. Wegener will report on the pathological-morphological findings.

Method

The content of thorium was determined by means of neutron activation analysis. The material obtained from the autopsy was divided into parts weighing about 1 to 2 grammes. After freeze-drying the samples were put into a polystyrene container. Then 32 samples, together with 8 standards, which contained different but known concentration of thorium, were irradiated in the rotating position of the research reactor Triga Mark I of the German-Cancer-Research-Center. The flux during the irradiation was $2.10^{12} \text{ n} \cdot \text{s}^{-1} \text{ cm}^{-2}$. The irradiation time lasted about 8 hours. The nuclear reaction equation for the irradiation and the decay of the thorium is as follows:



The neutron capture of thorium 232 causes the conversion to thorium 233, which decays with a half-life of 22 minutes to protactinium 233. This decays with a half-life of 27 days to uranium 233. This long half-life permits the activities of elements like sodium, bromine, chlorine etc. to decay. They were also produced by neutron irradiation and disturbed the detec-

tion of thorium. The rule is, that the quantitative measurements were done 14 days after the end of the irradiation. For this purpose the γ -rays, which resulted in the decay of protactinium, were measured.

By integration of the photopeak of the sample, and by comparing it with the photopeak of the standard, it is possible to determine the content of thorium in the sample. The measurements were done by a Germanium Lithium drifted detector or a 5" x 5" Na-J well type detector, depending on the content of thorium in the sample.

The limit of detection without chemical separation amounts to about 0.1 to 0.05 μg , depending on the phosphorus content in the sample. The margin error for this method is about 5%.

Results

Table I shows the minimal and maximal values of thorium content in the main organs. The large variation within the organs results from the different amounts of Thorotrast, which was given to the various patients, and the method by which it was stored within each patient. Due to the different concentrations even in the organs of one and the same patient, we did not calculate the mean values. In spite of these large variations it is possible to see regularities of the distribution of thorium. It is well known, that the main organs of the RES possess the highest concentration.

The second group contains the lungs, the pancreas, the adrenal gland, the gastro-intestinal tract and the bones. This group had an intermediate amount of thorium.

The third group, which stores very little amounts of thorium, contains the kidneys and the organs of the circulatory system. In all cases the brain shows the least concentration. The values of four cases were under the detection limit.

TABLE I

Thorium Concentration in Different Tissues

Tissue	^{232}Th ($\mu\text{g/g}$)
Spleen	5000 - 80000
Lymphatic nodes	80 - 98000
Liver	670 - 13800
Bone marrow	130 - 280
Adrenal gland	22 - 100
Lung	10 - 120
Testis	8 - 50
Gastrointestinal tract	5 - 21
Bone (compact)	4 - 21
Kidney	5 - 16
Prostate	4 - 13
Circulatory system	1 - 8
Brain	0.05 - 2.6

Because of the large variations within an organ we have tried to see whether a single detection could be representative of the content of thorium in the organ. For this purpose we have taken 10 random samples from 10 different livers. Each sample weighed about 1.5 grammes, and from each the concentration of thorium was determined. The results are shown in table II.

TABLE II

Thorium Concentration in Liver

Cases	^{232}Th ($\mu\text{g/g}$)	Factors
V 69 / 13	700 - 34300	49
V 69 / 29	1700 - 29000	17
V 69 / 1	2300 - 34000	15
V 69 / 3	1600 - 20000	13
V 69 / 25	2000 - 15000	8
V 69 / 26	380 - 3000	8
V 69 / 6	1200 - 7500	6
V 69 / 19	340 - 2300	5
V 69 / 17	1000 - 2900	3
V 69 / 23	900 - 2300	3

Here you see the range of variation of 10 samples for each case. The last column shows the quotient of the maximal and the minimal value. After these results we found it interesting to study the distribution of thorium in a complete liver. We wanted to see whether there was some regularity in the storing of Thorotrast. The liver which we chose, had a malignant hemangio-endothelium. The liver was divided into 952 parts in the following manner.

First it was cut into halves along the longitudinal line and then sliced into 20 sections in the vertical direction. The slices which we got in this manner were again divided into 7

horizontal sections and 14 vertical sections, where width and height allowed. From these divisions resulted 952 cubes with a side of 1.3 cm in length.

Fig. 1 shows the distribution of thorium in the horizontal section 3.

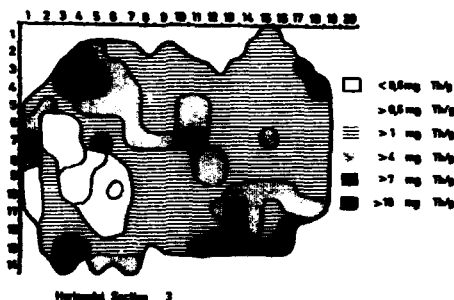


Fig. 1. Distribution of thorium 232 in the horizontal section 3

The right lobe of the liver shows a large area of low concentration. In this region the malignant tumour was located. In the area surrounding the tumour unhomogeneous deposits of thorium could be seen. In the left, tumour-free lobe the storing of thorium is irregular and unhomogeneous. Areas of very high concentration are found in the parenchyma of the liver as well as sporadically in the region of the capsule. A similar picture shows the other horizontal sections.

the skeleton and in bone marrow.

The results (table IV) show, as in the other two investigated organs, that there are considerable variations within the same portion of the skeleton, as well as between different portions. The highest concentration of thorium is found in the vertebral bodies, which contain a big part of the erythropoietic system. The measurements on the compacta of long bones show the least concentration of thorium.

It's surprising that the pure, red bone marrow of the femur has a lower concentration than the vertebral bodies. In the bone marrow we thus see considerable variations, which can be up to a factor of a hundred.

TABLE IV

Thorium Concentration in Bones

Bones	^{232}Th ($\mu\text{g/g}$)
Bone (compacta)	4 - 21
Bone marrow (red)	350 - 850
Bone marrow (yellow)	15 - 420
Vertebral bodies (cerv, dors, lumb.)	530 - 2320
Sternum	120 - 1060
Clavicle	31 - 240
Femur (caput)	14 - 1290
Ribs	4 - 920

Conclusions

The results which were presented in this report give the state of the distribution of thorium 20 to 30 years after injection of Thorotrast.

The unhomogeneous storing could be found in all organs. The variations in the liver, the lymphatic nodes and the bone marrow are considerable. From this we can draw the following conclusions:

1. The radiation injury is not only different between the different organs but also within one organ.

2. A calculation of the radiation dose of the total organ is difficult.

3. The concentration of thorium in a sample, which is obtained by needle biopsy, gives no clue of the weight of the Thorotrastose.

4. Conclusions about the development of the tumour in the liver of a Thorotrast-patient are not possible only on the basis of the quantitative determinations of the thorium.

Mr. Wegener will report, and discuss in detail the morphological findings of the examined samples during this meeting.

This study was supported by the Bundesministerium für Forschung und Technologie.

The Retention of the Daughters of Thorium 232
in the Soft Tissue in Animals.

by

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It is shown that 10% of an amount of Ra 228 injected i.v. is deposited in the bones in equilibrium with all of its daughters, and that no Ra 228 is found in the soft tissue. About 30 to 40% of an amount of Th 228 injected in animals will be deposited in the soft tissue. Of the daughters formed by Th 228 about 40% is found in the body of a sacrificed animal. Of this 40%, 15-20% has arisen from thoron which have diffused to the blood but have decayed before the blood has arrived to the lungs. Of the 60% of the Th 228 daughters which have left the living animal, about 15-20% has been exhaled as Rn 220, about 40% has been excreted as Ra 224 and about 5% has been excreted as Pb 212.

In the evaluation of the radiation dose to a tissue in which Thorotrast is deposited it is necessary to know to which extend the thorium-daughters will move away from the site where they have been formed.

The literature shows that a number of studies of the metabolism of the thorium-daughters have been performed in the Thorotrastpatients as well as in animals injected with Thorotrast, and we have learned that much information have been collected. But in order to get an even clearer picture of the fate of the single thorium-daughter I have thought it of interest to study their behaviour without the presence of the parent from which they will be continuously formed.

My attention has of course been drawn to the daughter-products living long enough to move from one tissue to another or to be excreted or exhaled. I have therefore concentrated my interest around the - from a biological point of view - long living nuclids i.e. the radiumisotopes 228 and 224, the thorium-isotope 228 and the leadisotope 212. Further thoron, the radon-isotope 220 is of interest - in spite of the short half life - as it as an inert gas rapidly will diffuse to the blood and partly will be exhaled in the lungs.

Experimental procedure.

The experimental animals were rabbits and all injections were given intravenously in an ear vein. The measurements of the amounts of the different nuclids were performed by repeated countings of the very high energetic γ -activity of thallium 208 and by the knowledge of the physical halflives of the nuclids.

Analysis of the radioactivity were performed both on living and on dead animals and on single organs. During the measurements the rabbits were held tight in a box, and in consecutive examinations the variation in the number of counts per unit time was within the statistical variability for successive countings. The dead animals and the single organs were kept at -20°C between the examinations.

In most of the experiments the daughters of thorium 232 were injected in equilibrium with each other in amounts which for thorium 228 were about 10^{-9} g/kg. The solution in which the thorium-daughters was injected was physiological saline. I want to emphasize this, as it may be of importance to know that no possibility existed for the nuclides to form complexes with any oxyacid e.g. citric acid, in the solution used for the injections.

In supplementary experiments either radon 220 was inhaled or lead 212 was injected.

Results.

From fig. 1 it will appear that after an initial period of about a month curves drawn for the numerical value of the γ -activity from thallium 208 decreases to about half the values after a period of little less than 2 years. In the figure curves are shown both from an animal killed after having been injected with the daughters of thorium 232 in equilibrium, and from an animal still alive. As the curves from this two animals decreases in an almost identical way, the curves tell that almost all of the radium 228 injected will be excreted soon after the injection. Along with radium 228 also radium 224 must be supposed to be

excreted.

Further the curves will show that the amount of thorium 228 which is not excreted during the first short period after the injection will stay in the tissue almost without any excretion. It must be kept in remembrance that thorium 228 will reach very near to equilibrium with its daughters in 20 days and that the measured activity of thallium 208 produced all the time therefore directly will give the amount of thorium 228 - at least in the dead animal.

Of the injected amounts of thorium 228 about 60 to 70% will be excreted in the first days after the injection, the rest 30-40% will, almost without excretion, be deposited in the animal.

In order to determine the distribution of the thorium 228 which is retained I have studied the γ -activity (from thallium 208) from different organs and at different times after an animal has been killed. The organ especially studied was the liver, as this organ because of its size was the easiest organ to handle in the measuring system at my disposal. The spleen showed a higher weight per cent for deposited thorium 228 but there were no distinct difference in the ways in which these two organs - as well as the lungs and the blood marrow retained the injected thorium-daughters, as time, after the injections had been given, grew on. The way in which thorium 228 is handled in these organs and up to a certain degree also how its daughters are handled will appear from fig. 2.

But before I go into details with the curves shown in the figure it may be worth mentioning that a part of the thorium 228

injected will be retained in the bones. In this case it will be deposited almost in equilibrium both with radium 228 from which it originates and with all of its daughters. The amount of thorium 228 in the bones will be about 10% of the amount deposited in the body. This amount of radium 228 with all the daughters almost in equilibrium with each other will stay in an almost constant amount in solid bone for a period of at least 2 years.

In the fig. 2 the curves are arranged in such a way that all of them are going through the same point 20 days after the sacrifice of the animals.

It will be seen that in relation to the amounts of the other thorium-daughters taken up in the first days after the injection a relatively large amount of lead 212 is taken up in the liver, as it is shown in curve 1 and 2.

Curve 3 gives the distribution of the daughters 3 weeks after the injection. Here the picture is dominated of an amount of thorium 228, almost no radium 224 and a small amount of lead 212. After the animal was killed the daughters grew up and we have the typical curve for the growth of the thorium 228 daughters measured by the amounts of the thallium-daughter.

For animal killed 7 and 28 weeks after the injection it seems that a part of the daughterproduct radium 224 and may be also parts of radon 220 and lead 212 produced in the liver by the disintegration will stay in this organ together with the mother. To my opinion this may indicate that a part of the thorium 228 had moved inside the cells. From the interior of a cell the passage of radium 224 to the blood may be more difficult than from the extracellular space.

Having thus seen a qualitative picture of the distribution of the daughters in the liver it will be of some interest to show the quantitative.

Table I.

Time after injection	per cent of Th 228 deposited in the liver of the amount injected
1 d	1%
1 week	
5 d	1%
3 weeks	30%
7 weeks	20%
28 weeks	8%
74 weeks	4%

It will be seen that during the first week only small amounts of the injected thorium 228 were found in the liver. In the third week the highest concentration was found and it will appear that this concentration will be reduced with time. This is found in the liver as well as in the spleen, the bone marrow and the lung.

Also in an other way it is possible to show that thorium 228 with time will have a more diffuse distribution. Animals were measured alive and again just after they had been sacrificed and exviscerated. In an animal which had lived for 3 weeks after the injection the number of counts decreased to half after the exvisceration while in an animal which had lived for 74 weeks after the injection a decrease of only one tenth was observed. (In this connection it must be kept in remembrance that an ani-

mal killed 3 weeks after the injection and not exviscerated - fig. 1 - will show an increase of $2 \frac{1}{2}$ times in the number of counts).

Up to now - after having shown that radium 228 is not deposited in the soft tissue - I have talked almost exclusively about thorium 228. However, the younger daughters are also of interest as there among them are four α -emitters. An increase in the number of counts arising from the γ -activity of thallium 228 after the animal was killed (as it is demonstrated in fig. I) shows that a part of daughters build up in the dead animal from the thoriumisotope. In the living animal they must have been excreted or exhaled.

I have tried to study the problem a little more thoroughly by indirect ways. First I have examined rabbits with thorium 228 and compared them with rabbits which had inspired air with radon 220 in it. The results are given in

Table II

γ -activity	Rn 220 rabbits	Th 228 rabbits
<u>blood</u>	$\frac{1}{2}$	$\frac{100}{1}$
<u>fat tissue</u>		
<u>muscle</u>	$\frac{1}{8}$	$\frac{16}{1}$
<u>fat tissue</u>		

It will be seen that - in the thorium 228-animals - almost no activity exists in the fat tissue; the tissue in which the solubility for thoron is 7-8 times higher as in other tissues. It can therefore be concluded that no thoron will be present in the blood of the thorium 228-animals after the blood has

passed the lungs. This would of course have had to be expected but it had to be proved.

A more interesting point is the behaviour of lead 212 the relatively long living daughter product of radon 220. Intravenously injected without its parents it will distribute in the following way:

Table III

Amounts of lead 212 in organs in relation to the amount adhering to erythrocytes.

Time between injection and analysis	per g.				
	erythrocytes	kidney	liver	spleen	lung
10 min.	1	2	1	1/5	1/5
1 h.	1	2	1	1/5	1/5
24 h.	1	1/2	1	1/5	1/5

1/5 of injected amount of lead 212 was excreted during 24 hours.

From the table it will be seen that lead 212 produced in the blood by the disintegration from thoron will adhere to several organs almost in the same amount as Hevesy and his coworkers has found it to adhere to the erythrocytes. Only a small part of the continuously formed leadisotope will be excreted.

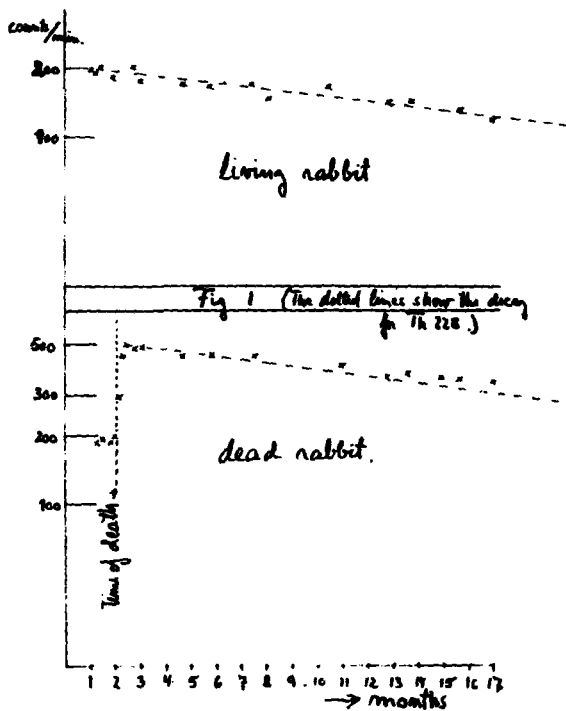
In animals which had lived for different periods from 3 weeks to 6-7 weeks after the injection of the daughters of thorium 232 I have found that about 5% of the total amount of the γ -energy from thallium 208, which the dead animal after equilibrium was found to possess, originated from lead 212 in the

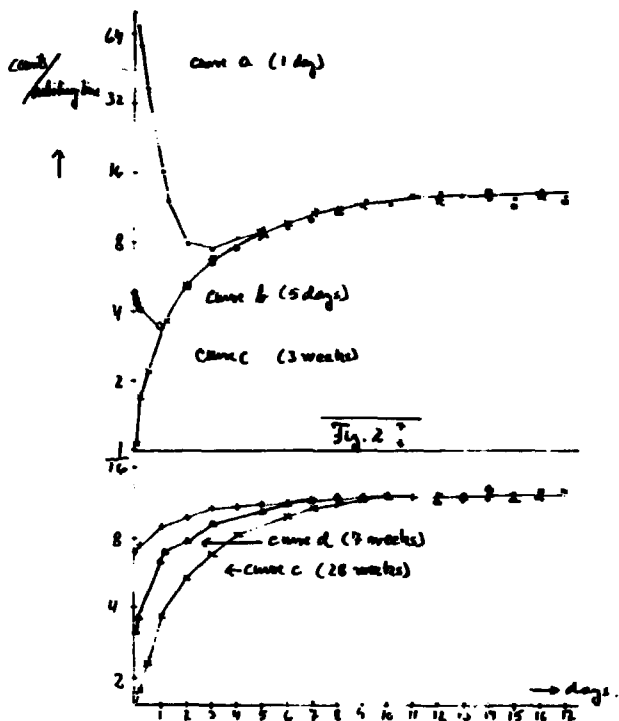
blood. If we take the observations given in table III into consideration we have to multiply the amount of lead 212 found in the blood and having arisen from decaying thoron in the blood by a factor of 3 to 4, to have the total amount of thoron which have decayed in the blood. From this observation and from a more detailed analysis of the figures for the increase in the γ -activity in the period after the sacrifice of the rabbits, I have arrived at the results given in table IV.

Table IV.

	percentage of nuclide found in the living animal in "Th 228 steady state"	percentage of nuclids excreted or exhaled
Th 228	about 100%	about 0%
Rn 224	about 60%	about 40%
Rn 220	about 40-45%	about 15-20%
Pb 212	about 40% of which almost the half originates from Rn 220 decaying in the blood	about 5%
Tl 208	about 40%	about 0%

This table summarise the results of my study.





Distribution of Thorotrast and its Daughter Nuclides
and Estimation of Absorbed Dose in the Human Organs.

by

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and

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SUMMARY

Thorotrast was intravenously injected into 80 SM mice. The volume administered per animal was 0.1 cc for one half of the samples and 0.5 cc for the remaining half. Twenty of the animals given 0.1 cc and an equal number of those given 0.5 cc were sacrificed three months after injection, and the gamma-ray activity in their organs was measured for the ensuing 30-day period under identical conditions for all samples. The rest of the samples were likewise sacrificed and examined five months after injection.

The build-up curves, plotted for each organ on the basis of these measurements, indicated that 19.9% of injected ThO_2 had been excreted and that 86% of the ThO_2 retained in the body had deposited in the liver, spleen and bone at the ratio of 67:22:11, respectively. The rate of thorium daughters excretion by these organs was measured at 76% for the liver, 79% for the spleen and 130% for the bone.

The absorbed dose of internal irradiation, estimated from the foregoing results, was much smaller than the values reported in the past. Incidentally, no significant difference of measurement results was noted between the animals given 0.1 cc of Thorotrast and those given 0.5 cc.

INTRODUCTION

It is well known that radioactive Thorotrast, once intravenously injected as a radiological contrast medium, remains in the body semi-permanently as deposits in the liver, spleen, bone and other organs belonging to the reticulo-endothelial system, the rate of its excretion by these organs being extremely low. The potential risk due to the resultant chronic internal irradiation is quite serious, to evaluate which it is necessary to

accurately estimate the dose of internal irradiation emitted by Thorotrast deposits in the organs, and this in turn makes it desirable that the distribution of the Thorotrast and its daughter products in the body be clarified.

For these purposes, the following experiments were undertaken.

EXPERIMENTS AND RESULTS

1. Distribution of ThO_2 :

Eighty SM mice were intravenously injected with 0.1 cc and 0.5 cc of Thorotrast each in equal numbers. Three months after injection, 20 of the mice given 0.1 cc and another 20 of those given 0.5 cc were sacrificed for immediate removal of their organs. The remaining 40 samples were likewise sacrificed five months after injection. In each case, the gamma-ray activity in the removed organs was measured by use of a scintillation counter over a period of 30 days subsequent to the organ removal. The gamma-ray activity levels of the organs, measured at the end of the 30-day period, were compared with the corresponding values for the controls to determine the amount of ThO_2 present in each of the organs.

As a result of this experiment, it was found that five months after injection, 19.9% of the ThO_2 had been excreted, and that 86% of the ThO_2 retained in the body had deposited in the liver, spleen and bone at the ratio of 67:22:11.

2. Distribution of daughter products:

In this experiment, the gamma-ray activity in the specimen organs was measured at 24-hour intervals during the 30-day period, and build-up curves were plotted from the measured values. Particular attention was paid to

ensure this and other experiments were conducted under identical conditions with respect to measuring methods and instruments.

a) Build-up curves of the liver and spleen:

In all of the specimen organs, the total gamma-ray activity level changed rapidly with the lapse of time. The gamma-ray activity in the organs immediately following removal was always lower than that in the same organs in a state of equilibrium. Also, the longer the duration from injection to sacrifice, the steeper became the build-up curves. These observations seemed to imply that the translocation of thorium daughter products from the liver and spleen increases with the length of time between injection and sacrifice.

b) Build-up curve of the bone:

For about three days after sacrifice, the total gamma-ray activity in the bone increased rapidly and then turned downward, thereafter continuing to decrease till it reached an equilibrium in about 30 days. This appears to suggest that the presence of larger amounts of thorium daughters in the bone than are produced there is due to the translocation of some daughter nuclides from the liver and spleen to the bone. Also, from the fact that the gamma-ray activity in the bone registered a sharp increase during the first three days following sacrifice, it is presumed that the decay products of ^{224}Ra include one particular nuclide that is translocated to other organs than the bone in large quantities. Judging by its half-life and by the build-up curve of the bone, this daughter nuclide is thought to be ^{212}Pb .

c) Distribution of daughter nuclides:

Based on an analysis of the build-up curves, the respective quantities of ^{224}Ra and its daughter nuclides in the organs were calculated by

using the formula: (Total gamma-ray activity in the organ at vivisection minus Total gamma-ray activity of Th / Total gamma-ray activity in the same organ 30 days after vivisection minus Total gamma-ray activity of Th) $\times 100$.

As a result, it was found that on the average 24% of Th daughter products was retained in the liver and 21% in the spleen five months after injection. Meanwhile, the amount of daughter nuclides in the bone was shown to have increased to approximately 130%, presumably owing to the redeposition of nuclides excreted from other organs.

Since ^{228}Ra and ^{224}Ra , being isotropic, are considered to exhibit identical behaviors in living organisms, it is thought that about 22% of ^{232}Th decay products, i.e. ^{228}Ra , ^{228}Ac and ^{228}Th , and about 5% of ^{224}Th daughters were retained in the liver. The corresponding figures were 21% and 4% for the spleen, and 119% and 144% for the bone.

In the case of daughter nuclides descending from ^{228}Th , the retention rate was calculated at 22% for the liver, 21% for the spleen and 119% for the bone.

3. Estimation of Absorbed dose in human organs:

In order to estimate absorbed dose in human organs, calculations were based on the following assumptions:

Approximately 20% of intravenously administered Thorotrast is excreted from the body immediately following administration, but excretion thereafter falls to a negligible level. About 90% of Thorotrast retained in the body is deposited in the liver, spleen and bone, the distribution ratio among these three organs being approximately 70:20:10. At the time of administration, Thorotrast contains ^{232}Th and ^{228}Th in

a state of equilibrium; other than the thorium series it does not contain radioactive substance. Out of the daughter nuclides produced from ThO_2 deposited in the liver and spleen following injection, 70% of ^{232}Th daughters, i.e. ^{228}Ra , ^{228}Ac and ^{228}Th , and 91% of ^{224}Ra and its daughters are excreted. Further, 70% of daughter nuclides from ^{228}Th is also excreted. On the other hand, a total of 120% is deposited in the bone because of translocation from other organs.

In the liver, spleen and bone, the self-absorption rate of alpha-emission is 50%, 75% and 75%, respectively (ref. Rotblat, J.), but self-absorption of beta-emission in these organs is negligible. The alpha- and beta-emission energies of the thorium decay series are shown in the table below:

Particle	Th	Ra	Ac	Th	Ra	Ra	Po	Pb	Bi	Po	Tl
Alpha (MeV)	4.0			5.42	5.68	6.28	6.78		6.05	8.78	
Beta (MeV)		0.012	1.11					0.33	2.25		1.79

Now, absorbed dose of internal irradiation in an organ where Thorotrast is deposited can be estimated by correcting with the assumptions given above the emission energy calculated by the usual method employed in nuclear physics. Let the constants K_{n1} , K_{n2} , ..., K'_{n1} , K'_{n2} , ... be the correction terms, and the amount of energy E which the organ absorbs when ^{232}Th disintegrates at the rate of one particle per second at $t = 0$ is expressed as:

$$E = \int_0^{11} Q_n \left\{ (K_{n1} K_{n2} \dots) \frac{\lambda_n N_n(t)}{\lambda_1 N_1(0)} + (K'_{n1} K'_{n2} \dots) \frac{\lambda_n N'_n(t)}{\lambda_1 N'_1(0)} \right\} dt \quad (\text{MeV})$$

If, for example, 10 cc of Thorotrast was intravenously administered to an average Japanese male (with a liver weighing 1,200 grams and a spleen weighing 100 grams), the internal irradiation dose absorbed in his liver during the first 10 years would be 81 rads of alpha-rays and 2 rads of beta-rays, while the corresponding figures for his spleen would be 138 rads (alpha) and 8 rads (beta), respectively. In his bone, meanwhile, the dose absorbed during the same period of time would be 33×10^{11} MeV of alpha-rays and

1×10^{11} MeV of beta-rays.

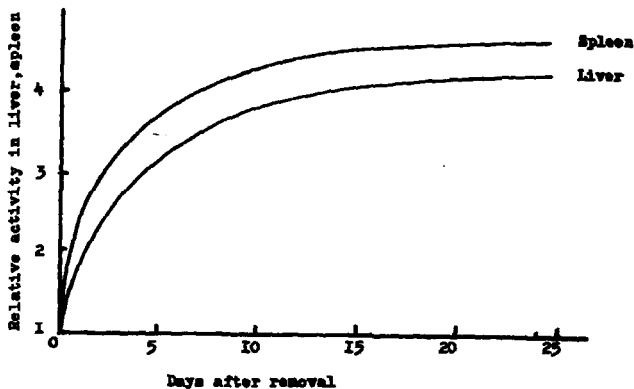
These values are much smaller than the values thus far reported.

DISCUSSION

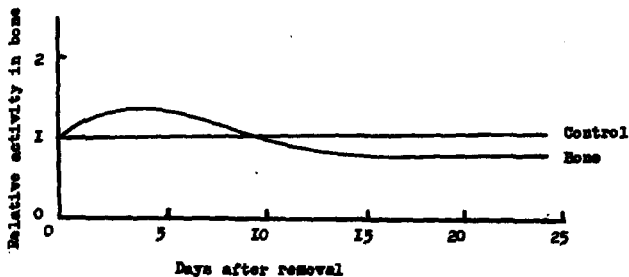
Various hazards to the vital organs due to the deposition of Thorotrast in the tissues have been reported to date. In studying the effects of internal irradiation by Thorotrast, the absorbed irradiation dose must be determined as accurately as possible, and the determination of the absorbed dose requires, among other things, clarification of the metabolic processes involving ThO_2 and its decay products. Although many studies have been published by researchers in this area, there have been few reports to date that deal specifically with such metabolic processes in the bone. In this sense, it is felt that some meaningful results have been obtained in the present study.

The absorbed dose reported in this paper is much smaller than the values reported in other studies. However, considering the very short track (20 to 30 microns) of alpha-rays emitted by nuclides within tissues, it is presumed that the absorbed dose in the immediate vicinity of the sites of Thorotrast deposition can be quite large.

* * * *



Build-up curves plotted from the measured gamma-ray activity of the liver and spleen of the mouse sacrificed five months after injection



Build-up curves of the bone and the control

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Thorium Series Radionuclides in Compact Bone of Thorotrast
Cases - Results of Measurements at IAEA

by

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Abstract

The activity of thorium-series radionuclides in compact bone of Thorotrast cases is of interest because of the possibility of extracting skeletal dose-effect relationships in this population for comparison against similar data from populations containing ^{226}Ra , ^{228}Ra , or ^{224}Ra . Estimates of activity levels in compact bone can be obtained directly from measurements on such tissue collected at autopsy, or indirectly from measurements on the release of radium isotopes from the primary Thorotrast deposits in other tissues combined with calculations of skeletal deposition based on the new ICRP model of alkaline earth metabolism in adult humans. Autopsy samples from 5 Thorotrast cases have been measured in the laboratory of the IAEA. The results of these measurements suggest that: (1) ^{232}Th concentrations (nCi/g wet tissue) in compact bone are about 1 % of those in liver, (2) ^{228}Ra and ^{224}Ra translocate to compact bone in amounts about equal to or less than those predicted by the ICRP model, and (3) ^{228}Th translocates to compact bone at dosimetrically inconsequential levels. The measured compact bone activities reside near the low end of the spectrum of previously reported results.

Key words

Thorotrast	^{228}Ra	dose
^{224}Ra	bone	

I. Introduction

A very small part of the Thorotrast injected into the blood of a person is presumably deposited in the marrow-free skeleton, and some of the radionuclides descended from thorium are deposited in the skeleton following their escape from the primary Thorotrast deposits elsewhere in the body. Attention has been drawn, particularly by Marinelli (e.g., Marinelli and Lucas, 1962), to the possible toxicological consequences of the resultant skeletal irradiation. Thus, it has been suggested that the average skeletal dose rates in Thorotrast cases may be a substantial fraction of the average skeletal dose rate associated with a ^{226}Ra deposit of 0.1 μCi , the long-standing maximum permissible burden of this reference radionuclide. If so, it has been further suggested that bone cancer incidence rates in the world's population of Thorotrast cases might help to confirm or to disprove that such skeletal dose rates are innocuous.

The then available data on skeletal dose rates in Thorotrast cases were summarized by Marinelli at the 1965 IAEA-WHO meeting on The Dosimetry and Toxicity of Thorotrast (see Marinelli (1968) or Dudley (1967)). Since then, new data on skeletal radioactivity in Thorotrast cases continues to be collected, the means of interpreting such data have been greatly advanced by publication of the ICRP's new and detailed model of alkaline earth metabolism in adult man (Marshall et al., 1973), and interest in the subject has been heightened by the appearance of dosimetric and epidemiological data on persons injected with ^{224}Ra (Spiess and Mays, 1970).

The purpose of this paper is to add to the existing literature the observations made at our laboratory on radionuclide concentrations in compact bone of Thorotrast cases, and to compare them with predictions of the ICRP model.

II. Measurements and analysis of measured data

A. Autopsy samples

The work performed at our laboratory relevant to activity in compact bone consists primarily of measurements on autopsy samples from 5 Thorotrast cases. For only 3 of these were measurements performed on the bones themselves, but useful data on the escape of the bone-seeking thorium descendants from liver and spleen were obtained from all 5 cases.

Autopsy samples have reached the laboratory anywhere from hours to days after death of the subject. Bones were usually sawed longitudinally with a hacksaw, scraped free of marrow and trabeculae, and cleaned with a water jet. Other tissues were processed only to the extent of dividing them with a knife so as to fit them into containers. All samples whose measurements are reported here were weighed in the wet state and packed into tin cans (9 cm ϕ x 12 cm). Paper stuffing was added if necessary to immobilize the samples in the cans, and the cans were then sealed. They were kept thereafter in a deep freeze unit except during counting.

The activity in the canned samples was measured with a NaI(Tl) detector (20 cm ϕ x 10 cm) coupled to a multichannel analyzer. Geometry of measurement was individually selected with priorities in the following order when compromises were necessary: (1) reproducible conditions, (2) statistically adequate counting rates, and (3) minimum geometrical ambiguity in comparing samples against standardized reference sources to establish absolute activities. Cans containing bone samples, whose activity was always marginal, were usually positioned directly on the crystal face, while those containing liver or spleen samples were counted at a distance of about 35 cm from the crystal face.

Reference standards consisted of aged (1906) thorium having an equilibrated decay chain, and ^{228}Th plus descendants. Two aged thorium standards were used, the first a thin layer and the second a slender cylinder. The ^{228}Th standards were the residue of evaporated droplets of ^{228}Th solution heat-sealed between thin sheets of plastic.

During measurement these reference standards were variously positioned in cans partially or completely filled with sugar to simulate the sample mass, or in Preswood phantoms. Differences between samples and standard with respect to geometry and absorption were sufficient to give appreciable errors in absolute activity estimates for samples such as bone that were positioned on the crystal face. However, they were not so large as to cause important errors in estimates of parent-daughter activity ratios, and it is these ratios that are of predominant interest.

Deduction of the absolute activities and the activity ratios (at death) of the thorium series radionuclides in each sample was based on analysis of the spectral peak at 0.93 MeV attributable to the 0.90 and 0.96 MeV γ rays of ^{228}Ac , and the peak of the 2.62 MeV γ ray of ^{208}Tl . The contribution of the 2.62 MeV γ rays to the counts at 0.93 MeV was stripped out

by reference to the spectrum of the ^{228}Th standard (containing no ^{228}Ac). The absolute activity of ^{228}Ra was determined by comparison of the net 0.93 MeV counts of sample and analogously positioned standard within days or weeks of death. The activity ratio $^{228}\text{Ra}/^{232}\text{Th}$ was calculated from the growth of ^{228}Ra during subsequent years. The activity ratio $^{228}\text{Th}/^{228}\text{Ra}$ was established by comparison of the relative abundance of counts from "0.93 MeV" and 2.62 MeV γ rays at about 1 month after death. The activity ratios $^{224}\text{Ra}/^{228}\text{Th}$ and $^{212}\text{Pb}/^{224}\text{Ra}$ were computed from the changes in the relative abundance of counts from "0.93 MeV" and 2.62 MeV γ rays during the first month after death, using the Bateman equations. In most cases the samples were obtained more than a day after death, so that assay of ^{212}Pb was impossible.

A primary issue is the assignment of realistic estimates of standard deviations, allowing for errors of all origins, to the quantities deduced from the measurements. Both absolute activities and activity ratios are given in the subsequently tabulated results in order that their respective errors may be separately displayed. The error in absolute activity is generally proportionately larger since it includes a contribution from geometrical ambiguities in comparison with the standards, while the errors in the ratios are substantially or entirely free of such contributions. Inevitably the error estimates contain an appreciable element of subjective judgement to allow for the numerous uncertainties beyond counting statistics: weighting of discrepant results, allowance for shifts of background, allowance for differences between standards and samples, etc. It is likely that the data collected in further measurements on these and other samples, and the insight they give into errors, will lead us to adjust both the results and the error estimates in our next compilation. However, it is not likely that these adjustments will be so large as to give conclusions differing significantly from those drawn in this paper.

B. Living subjects

On about 75 living Thorotrast cases we have measured the total body burden of ^{228}Ra (via the 0.90 and 0.96 MeV ^{228}Ac γ rays) and ^{212}Bi (via the 2.62 MeV ^{208}Tl γ ray), and the profile of ^{212}Bi activity along the length of the body. The total body activity measurements were performed in the IAEA whole-body counter, with a 20 cm ϕ x 10 cm NaI(Tl) detector scanned along the length of the subject reclining first prone and then supine

(Dudley and ben Haim, 1968). The profile scan was performed with the same instrument using a slit collimator over the detector face (Parr et al., 1972). While in general these results are of only peripheral relevance to skeletal activity, the measurements we were able to make on 4 of the 5 cases who subsequently came to autopsy have helped to round out the picture deduced from the fragmentary sets of autopsy samples obtained.

III. Results

Case history data on the subjects who came to autopsy are given in Table 1, activity concentrations as of death in the autopsy samples relevant to skeletal activities are given in Table 2, and activity data for the whole organs and for the living bodies are given in Table 3. In Table 2 each column labeled "R" gives the ratio of the activity of the descendant nuclide on the right to that of the predecessor on the left, as of the time of the subject's death. Liver samples A, B, C, etc. refer to separate subdivisions of the liver as contained in individual cans. As yet insufficient time has elapsed since death of case Z to allow an assessment of the ^{232}Th activity. In Table 3 the data for the ^{212}Bi activity in the body regions "upper abdomen" and "injection site" are taken from the profile scan. They represent the activity in a volume including the full width and depth of the subject and about 37 cm of his length at the regions in question; they thus include respectively the liver-plus-spleen and the Thorotrastoma (if any), and in addition neighboring tissues. All errors quoted are standard deviations representing the author's best estimate of composite errors derived from all sources.

IV. Deductions

A. Measurements on bone

The data directly relevant to activities in compact bone free of red marrow are the results given in Table 2 for the 6 such samples (one from S, 2 from H, and 3 from Z), and the related values in Table 3 for activity in the entire available organs or in the living bodies. (The femur head of H and the ribs of Z contain red marrow, and their activity patterns are typical of those expected from Thorotrast itself in the marrow.)

It is apparent that all radionuclides are found in essentially all of these samples (although in many cases near the lower limit of sensitivity of

the assay method used) at a concentration of the order of 0.5% - 5% of that in liver. Beyond the absolute activities, the ratios of activities should also be important in that they may reveal the mechanism by which the respective radionuclides come to be deposited in bone, hence in which of its component structures they are located, hence how toxic they are likely to be. There are probably no data available on the fractional retention, at the sites of ^{232}Th localization in bone, of the ^{228}Ra born therein. This ^{232}Th may well be in the form of Thorotrast particles, in which case the ^{228}Ra retention probably would resemble that observed in Thorotrast deposits in soft tissue. For present purposes this fraction is taken as 0.4 ± 0.1 , a range encompassing all the values in Table 2 for Thorotrast in soft tissue. One may probably assume without great error a fractional retention of unity for each subsequent radionuclide born in bone from chronic depositions of the parents, although this would be less nearly true if a substantial fraction of the activity were in Thorotrast particles.

Upon adoption of these assumptions, it is possible to calculate for the compact bone samples in Table 2 the concentrations of the radionuclides in excess of those expected to result from the concentrations of their predecessors. These excess concentrations are attributable to escape of the respective radionuclides from the primary Thorotrast deposits and their redeposition from the blood into the skeleton. The inferred excess concentrations are shown in Table 4, under the column heading "observed". (The standard deviations attached to these inferred excess activity concentrations have been propagated from those recorded in Table 2 under recognition that part of the error in parent and daughter activities is correlated, reflecting uncertainties in the absolute activity of the chain, and that this component should not be included twice.)

From Table 4 it appears that ^{228}Ra and ^{224}Ra do show excess activity concentrations above those of their predecessors, but the amounts are so low that they are not always distinguishable from zero. ^{228}Th , however, shows no excess activity, and the limits are sufficiently small that the toxic effect of migrated ^{228}Th in the compact bone of these cases could presumably be ignored in comparison with the effects of other radionuclides.

B. Measurements on primary deposits of Thorotrast

From measurements on the primary deposits of Thorotrast in these cases the amounts of ^{228}Ra , ^{228}Th , and ^{224}Ra continually infusing from these

deposits into the blood can be deduced, and predictions can be made (chiefly via the ICRP model of alkaline earth metabolism) for the amounts of these radionuclides deposited in compact bone.

Predictions for two (H and Z) of the three cases from whom bone samples were obtained are complicated by the presence of substantial para-vascular deposits at the site of injection, and these apparently release ^{224}Ra , at least, to a lower extent than does liver. The fraction of Thorotrast at the sites of injection is not well known, and the collection of other tissues (liver for Z, red marrow for both) is incomplete so as to prevent estimation of the magnitude of the deposit by the difference between whole-body activity and the activity in all other deposits. Nevertheless, reasonably good estimates of the total amounts of ^{228}Ra and ^{224}Ra infusing into the blood of the 3 cases can be made as follows. ^{228}Ra : cases S and H - whole body ^{228}Ra activity taken from measurements on the living subjects, whole body ^{232}Th activity estimated by assuming R for $^{228}\text{Ra}/^{232}\text{Th}$ in the whole body equals that measured in liver; case Z - ditto, using R from case H. ^{224}Ra : case S (negligible deposit at injection site) - whole body ^{228}Th equals whole body ^{228}Ra , fraction of ^{228}Ra at injection site estimated from profile scan, R for injection site equals 0.91 (as in H Thorotrastoma) and for rest of body equals 0.75. With these methods the daily rate of infusion of the radium isotopes into the blood is found as in Table 5, probably with a standard deviation of 20% - 25%.

From these data on the radium isotopes, the ICRP model (Table 36 in Marshall et al., 1973) predicts directly the resultant concentration of activity in compact bone, as recorded in Table 4 under the column heading "ICRP prediction". (The standard deviations given in these columns are to be understood as reflecting estimated errors in the infusion rates, but none of the inaccuracies inherent in the model.)

The observations and predictions in Table 4 appear to be not grossly inconsistent. However, in view of the experimental errors the only conclusion that can be drawn with some confidence is that the observations are about the same as or smaller than the predictions. If the actual ^{228}Ra and ^{224}Ra levels were substantially higher than predicted, they would be clearly visible above the experimental errors.

^{228}Th metabolism is not covered by the ICRP model, but the issue of its translocation may still be considered. In Table 2 the values of R for $^{228}\text{Th}/^{228}\text{Ra}$ in the livers is near 1.00, implying very little escape, but

values as low as 0.90, implying 10 % escape, cannot be excluded. If indeed 5 % escaped and 70 % of this quantity (from animal experiments, Stover et al., 1960) were deposited on bone surfaces, then the excess ^{228}Th concentrations expected in Table 4 would be about 1.5 pCi/g for all 3 subjects. Since this value is much higher than that observed, it is probable that less than 1 % of the ^{228}Th born in Thorotrast escapes into the blood in a bone-seeking form.

V. Conclusions

Our observations suggest that: (1) The concentrations of thorium series radionuclides in the compact bones of Thorotrast cases are of the order of 1 % of those in the liver. (2) The radium isotopes released from primary Thorotrast deposits (about 60 % of the ^{228}Ra and 25 % of the ^{224}Ra born there) are deposited in compact bone in concentrations about equal to or less than predicted by the new ICRP model for metabolism of alkaline earths. (3) So little ^{228}Th migrates from the primary Thorotrast deposits to the compact bone that its contribution to toxicity there can probably be neglected.

It must be recognised that these conclusions rest upon only our own observations, which are small in number and were made near the limit of sensitivity of our technique. Nevertheless, they are reasonably robust as upper limits. It may be hoped that upon conclusion of this meeting a new synthesis of all existing data on skeletal activities and dose rates will be initiated.

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Table 1

Case History Data on Subjects Autopsied

<u>Case</u>	<u>Dates</u>			<u>Site of Injection</u>
	<u>Birth</u>	<u>Injection</u>	<u>Death</u>	
S	1904	1940	1965	Femoral arteries
H	1906	1942	1969	Femoral artery
W	1910	1940	1966	Femoral arteries
F	?	?	1969	?
Z	1903	1940	1973	Femoral arteries

Table 2
Activity Concentrations at Death in Selected Autopsy Specimens
(Estimates as of April 1973)

Sub-ject	Sample	Spec (g)	Activity Concentrations: Absolute (pCi/g wet) and Ratio (R) to Predecessor									
			^{232}Th	^{235}U	^{238}Pu	^{239}Pu	^{240}Pu	^{241}Pu	^{242}Pu	^{243}Am	^{244}Am	^{245}Am
A	Liver A	538	380E38	0.37E-02	19E29							
	Liver B	510	230E36	0.36E-02	8E28							
	Liver C	598	230E35	0.36E-02	8E28							
	Liver D	568	300E38	0.36E-02	10E29							
	Σ (Liver A-D) (whole organ)	2804	11E37	0.36E-02	11E29	0.95E-04	11E26	0.76E-03	8E26			
	Spleen (whole organ)	109	1730E90	0.15E-02	60E27	0.96E-04	58E27	0.73E-03	66E27			
	Pancreas (narrow and trabeculae removed)	220	1.7E-05	1.3E-01	2.3E-05	1.0E-05	2.3E-05	1.8E-02	4.1E-09			
	Liver (whole organ)	2394	800E12	0.39E-02	78E4	0.97E-03	7E24	0.75E-02	5E24	0.56E-04	13E4	
	Spleen (whole organ)	111	1000E45	0.15E-01	33E29	0.97E-04	3E218	0.82E-03	7E27	0.66E-06	18E27	
	Thyroidectomy	299	380E13	0.66E-02	27E27	0.96E-02	80E18	0.91E-02	23E10	1.03E-06	26E27	
B	Pancreas head (with red marrow)	249	3E28	0.9E-02	1E24	0.98E-04	1E24	0.91E-04	1E24	1.0E-03	1E24	
	Pancreas and spleen head (narrow and trabeculae removed)	374	2.4E-08	0.6E-01	1.6E-05	0.99E-03	1.6E-05	1.0E-04	1.7E-05	1.0E-06	1.7E-05	
	Pancreas distal end and spleen both ends (with yellow marrow)	808	0.6E-01	1.1E-015	0.5E-01	1.0E-07	0.5E-01	1.0E-03	0.9E-02			
	Liver (whole organ)	1294	8E1	0.38E-02	2.9E-03	0.91E-05	2.7E-03	0.78E-03	1.9E-02			
	Spleen (whole organ)	65	2E23	0.15E-02	9E-09	0.91E-06	8E1	0.8E-01	7E1			
	Liver A	495	1E25	0.39E-01	50E1.5	0.96E-02	48E1.5					
	Liver B	472	13E24	0.36E-01	10E22	0.96E-02	9E22					
	Liver C	495	27E28	0.37E-01	9E22	0.96E-02	9E22					
	Liver D	448	28E29	0.37E-01	10E22	0.96E-02	10E22					
	Liver E	441	20E27	0.37E-01	9E22	0.99E-02	7E22					
C	Σ (Liver A-E) (2/3 of organ)	2261	230E9	0.37E-01	8E22	0.95E-02	8E23					
	Spleen (whole organ)	211	11E2E25	0.38E-01	43E29	0.93E-02	9E23					
	Liver A	534			17.6E-04	1.0E-03	18.2E-06					
	Liver B	508			35.8E-06	1.0E-03	36.4E1.2					
	Liver C	547			46.5E-09	1.0E-03	48.3E1.6					
	Liver D	476			42.4E-08	0.97E-03	41.2E1.3					
	Liver E	499			26.8E-07	0.99E-04	25.4E1.3					
	Σ (Liver A-E) (2/3 of organ)	2363			34.2E-08	1.00E-02	34.2E1.3	0.70E-02	24.1E1.3			
	Spleen (whole organ)	28			2800E100	0.91E-03	2900E100	0.96E-02	2600E100			
	Pancreas head (narrow and trabeculae removed)	260			8.7E1	0.98E-06	8.5E1	1.0E-05	8.7E1			
D	Pancreas shaft (narrow and trabeculae removed)	276			2.9E-04	0.96E-06	2.9E-04	1.1E-05	3.3E-05			
	Pancreas distal end (narrow and trabeculae removed)	222			1.6E-02	0.95E-06	1.5E-02	2.1E-04	3.1E-09			
	Spleen (with marrow)	72			8E24	0.94E-06	8E24	0.98E-05	2E24			

Table 3

Activity (mCi) in Tissues (at death)
and in Bodies (living) of Subjects Autopsied

<u>Subject</u>	<u>Sample</u>	<u>228_{Ra}</u>	<u>228_{Th}</u>	<u>224_{Ra}</u>	<u>212_{Bi}</u>
S	Autopsy sample				
	Liver	254±13	241±13	183±13	
	Spleen	66±3	63±3	50±3	
	Thorotrastoma				
	Living body				
	Upper abdomen				243±25
	Injection site				30±9
	Whole body	364±25			300±21
H	Autopsy sample				
	Liver	186±10	180±10	135±10	
	Spleen	37±1	36±1	30±3	
	Thorotrastoma	80±2	77±3	70±3	
	Living body				
	Upper abdomen				220±22
	Injection site				107±10
	Whole body	463±32			348±24
F	Autopsy sample				
	Liver	3.8±0.4	3.5±0.4	2.5±0.3	
	Spleen	0.59±0.06	0.54±0.07	0.45±0.07	
W	Autopsy sample				
	Liver	197±5	187±7		
	Spleen	99±2	92±3		
	Living body				
	Whole body	519±36			462±32
Z	Autopsy sample				
	2/3 Liver	81±2	81±3	57±3	
	Spleen	78±3	71±3	68±3	
	Living body				
	Upper abdomen				196±20
	Injection site				168±17
	Whole body	481±34			420±29

Table 4

Inferred Concentrations of Migrated Radionuclides in Compact Bone
(pCi/g wet)

Case	Bone	^{228}Ra		^{228}Th	^{224}Ra	
		ICRP		Observed	ICRP	
		Observed	Prediction		Observed	Prediction
S	Femur shaft	1.6 \pm 0.4	1.2 \pm 0.2	0.0 \pm 0.1	1.8 \pm 0.5	1.3 \pm 0.3
H	Femur, tibia mid-shaft	0.5 \pm 0.3	1.3 \pm 0.3	-0.02 \pm 0.06	0.1 \pm 0.1	1.4 \pm 0.3
	Femur distal end, tibia both ends	0.3 \pm 0.2	1.3 \pm 0.3	0.02 \pm 0.04	0.4 \pm 0.1	1.4 \pm 0.3
Z	Femur head	<9 \pm 1	1.4 \pm 0.3	-0.1 \pm 0.2	0.2 \pm 0.4	1.2 \pm 0.3
	Femur shaft	<2.9 \pm 0.4	1.4 \pm 0.3	-0.1 \pm 0.2	0.4 \pm 0.4	1.2 \pm 0.3
	Femur distal end	<1.6 \pm 0.2	1.4 \pm 0.3	-0.1 \pm 0.1	1.6 \pm 0.5	1.2 \pm 0.3

Table 5

Estimated Rates of Infusion of ^{228}Ra and ^{224}Ra into Blood
from Thorotrast Deposits

<u>Subject</u>	<u>^{228}Ra</u>	<u>^{224}Ra</u>
S	0.21 nCi/d	16 nCi/d
H	0.23	18
Z	0.24	15

The Skeletal Dose from ^{224}Ra Following Intravascular
Administration of Thorotrast*

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Abstract

With the use of a set of "best estimates" of the distribution of ^{232}Th and its daughters in the marrow-free skeleton following intravenous administration of Thorotrast, the dose to bone from "translocatable" ^{224}Ra has been calculated. "Translocatable" ^{224}Ra is that radium created *in vivo* that is free to translocate, i.e., equivalent to systemically injected radium. The accumulated dose to bone from this ^{224}Ra 25 years after injection of 25 ml of Thorotrast is of the order of 25 rads. A linear dose-effect relationship for the appearance of bone tumors in man has been postulated from the observed tumor incidence in the series of patients injected with ^{224}Ra in Germany. This linear hypothesis predicts more bone tumors in Thorotrast cases than are observed, implying either that the relationship is not linear at low doses, or that at very low dose rates the effect per rad is lower than predicted.

Key words: Thorotrast
 ^{224}Ra
Dose
Dose Rate
Bone Tumors

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In recent years the biological consequences of the injection of ^{224}Ra into human subjects have become apparent. Spless and Mays⁽¹⁾ have documented the appearance of bone sarcomas in these cases, and from their calculations of average skeletal dose they have postulated that the number of these malignancies may be related to dose in a linear fashion. Specifically, they have predicted that, for adults, the cumulative incidence of bone sarcoma from ^{224}Ra injections is

$$0.90\% \text{ per } 100 \text{ rads.}$$

Subsequently, following a suggestion of Müller, they re-examined their data to determine whether protraction of the period over which the short-lived ^{224}Ra was injected would tend to increase its effectiveness per rad. They found⁽²⁾ that the effect per rad apparently did increase as the injection span became longer, such that the effectiveness (% incidence of bone sarcomas per 100 rads average skeletal dose) for an injection span of m months could be expressed, for adults, as

$$\text{Effectiveness} = \frac{0.3\%}{100 \text{ rads}} + \frac{1.4\%}{100 \text{ rads}} \left[1 - e^{-0.09 m} \right].$$

This expression approaches its limiting value of

$$1.7\% \text{ per } 100 \text{ rads}$$

for injection periods longer than 5 years.

In their study of over 600 adults who received ^{224}Ra , the lowest skeletal dose at which a tumor was observed was 90 rads. This was not an isolated instance, they point out, because other sarcomas were seen at 106 rads and 129 rads.⁽¹⁾

The purpose of this paper is to examine the doses delivered to the skeletal system from ^{224}Ra born in the decay chain of the systemically injected radioactive contrast medium, Thorotrast. Specifically, we want to see if the low doses delivered by ^{224}Ra to the skeleton of Thorotrast cases can be used to test the validity of the concept that a linear relation exists between dose and effect at low doses and low dose rates.

The dosimetry of Thorotrast is exceedingly complicated, due to the multiplicity of short-lived daughters, whose pathways through the human body are difficult to map. These complexities will be reviewed only as much as necessary to elucidate the behavior of ^{224}Ra . That quantity of ^{224}Ra that is free to translocate will be estimated, and its contribution to the skeletal dose calculated; this skeletal dose will then be used to find the expected occurrence of bone sarcoma in the Thorotrast populations under study.

An ampule of Thorotrast contains ThO_2 in the ratio 25 g ThO_2 in 100 ml Thorotrast, or about 22 g thorium per 100 ml. (These figures refer to Thorotrast produced in the United States; that produced elsewhere may contain somewhat less thorium.) Depending upon its past history, the

$^{228}\text{Th}/^{232}\text{Th}$ ratio of this material lies between 0.2 and 1.0.⁽³⁾ For reference, 22 g of thorium contains 2.42 μCi of the 1.4×10^{10} year half period ^{232}Th , and between 0.48 μCi and 2.42 μCi of the 1.9 year half period ^{228}Th . The quantity of ^{228}Th and of ^{228}Ra (half period 5.7 years) present in the ampule before injection (all radium is probably eliminated at the time of preparation) is a function of the initial $^{228}\text{Th}/^{232}\text{Th}$ ratio and the time since preparation.

Since each microcurie of injected ^{224}Ra delivers an average skeletal dose of only 0.2 rad to an adult,⁽¹⁾ and since it is evident that the quantity of 3.62-day ^{224}Ra present in, say, a 50 ml Thorotrast injection is not likely to exceed 1 μCi , this quantity, even if it were free to be carried via the blood to bone, would deliver only an insignificant skeletal dose. We will concern ourselves with the ^{224}Ra produced *in vivo*, and examine its distribution after a steady state distribution of the Thorotrast daughter products has been achieved.

It is well to recall at this time that Thorotrast is a colloidal suspension, and that the ThO_2 particles have sizes the order of 100 Å. The *in vivo* deposits are, of course, aggregates, and thus much larger. It has been postulated by Parr, *et al.*⁽³⁾ that alpha recoil processes may liberate daughter products from these particles, and since two alpha decays (^{232}Th to ^{228}Ra , ^{228}Th to ^{224}Ra) precede the formation of ^{224}Ra , it does have opportunity to escape from within the aggregate. Since the ratios of the various daughter products to the parent ^{232}Th are considerably less than unity in many organs at long times after injection, there is no doubt that a considerable fraction of the daughter products do escape from the aggregates.

Parr, *et al.*⁽³⁾ have produced a set of estimates of the steady state distribution of Thorotrast daughters in various organs, based on an original set of "best estimates" by Marinelli.⁽⁴⁾ Relative to our problem, the figures in Table I from these estimates are instructive.

TABLE I

Thorium-Series Activities in Various Organs
(50 ml Thorotrast Injected Intravascularly)

(from Parr, *et al.*⁽³⁾)

Organ	Wet Weight g	Nanocuries in organ at steady state			
		^{232}Th	^{228}Ra	^{228}Th	^{224}Ra
Whole Body	70,000	1,250	625	625	580
Liver	1,700	860	430	390	270
Spleen	150	210	105	95	67
Red bone marrow	1,500	100	25	30	20
Skeleton (marrow free)	7,000	15	25	30	50

It is also instructive to consider this set of "best estimates" in terms of the ratios of the radium isotopes to ^{232}Th and to ^{228}Th . These ratios are tabulated in Table II for several relevant organs.

TABLE II

Ratios of the Radium Isotopes to their Parent
Thorium Atoms in Selected Organs

Organ	$^{228}\text{Ra}/^{232}\text{Th}$	$^{224}\text{Ra}/^{232}\text{Th}$	$^{224}\text{Ra}/^{228}\text{Th}$
Liver	0.5	0.31	0.69
Spleen	0.5	0.32	0.71
Red bone marrow	0.25	0.2	0.67
Skeleton (marrow free)	1.7	3.3	1.7

One could assume from the information in Tables I and II that approximately 30% of the ^{224}Ra formed *in vivo* is associated with ^{232}Th , and we will therefore assume that 70% of the ^{224}Ra is not bound in Thorotrast aggregates.

Very little ^{232}Th is found in the marrow-free skeleton, and it is likely that this thorium is not in aggregates, but deposited in bone as thorium atoms. If this were the case, no ^{224}Ra would be associated with ^{232}Th in bone. At the other extreme, if all of the ^{232}Th (15 nCi) in the marrow-free skeleton were colloidal, then with this thorium would be associated 5 nCi ^{224}Ra . So, of the 50 nCi of ^{224}Ra in the marrow-free skeleton, we assume 5 nCi or less (perhaps none) are in aggregates.

Similarly, it appears as if 50% of the ^{228}Ra formed *in vivo* is associated with ^{232}Th , so perhaps as much as 7.5 nCi ^{228}Ra in the marrow-free skeleton is bound in aggregates. This is the maximum estimate; it is possible that none of the ^{228}Ra is in aggregates.

The remainder of the ^{228}Ra (between 17.5 nCi and 25 nCi) we will assume is deposited in bone. Since this is a long half life isotope of radium, it will be distributed throughout the mineral volume. As it decays to ^{228}Th and in turn to ^{224}Ra , it is likely that neither of these daughters is translocated from their site of origin. Thus, this ^{224}Ra (between 17.5 nCi and 25 nCi) does not decay in the same locations as would injected ^{224}Ra .

It should be noted that there is more ^{228}Th in the marrow-free skeleton than ^{228}Ra , so that there may be a ^{228}Th deposition in bone not associated with ^{228}Ra . Since ^{228}Th deposits on bone surfaces, the ^{224}Ra born of this ^{228}Th deposit might be expected to be free to translocate, and indeed experimental evidence exists that indicates that this is the case.⁽⁵⁾ Thus it is only the ^{228}Ra deposition in the bone volume that prevents ^{224}Ra subsequently created from translocating, for ^{224}Ra born of ^{228}Th in thorium-like deposition patterns in bone is free to translocate.

Thus we will assume that ^{224}Ra not in aggregates and that not born of ^{228}Ra in the mineral volume will decay in bone at the same locations as injected ^{224}Ra . How much is this? It could be as much as 50 nCi (total in bone) less 5 nCi (in thorium aggregates) less 17.5 nCi (created in the mineral volume), or 27.5 nCi. It might be as little as 50 nCi (total in bone) less 0 nCi (in thorium aggregates) less 25 nCi (created in the mineral volume), or 25 nCi.

We will assume that there are about 25 nCi ^{224}Ra in bone following a 50 ml Thorotrast injection which could be thought of as behaving similarly to injected ^{224}Ra . One might ask, how could this low a level of ^{224}Ra be thought to be carcinogenic, when the lowest dose case (90 rads) to have a sarcoma in the Spiess-Mays' series received 448 μCi ^{224}Ra ? It is instructive, before we consider the actual dosimetry, to ask how many ^{224}Ra atoms decay on bone surfaces in each case. In the lowest-dose Spiess-Mays' case, an adult, for whom the authors assumed 1/10 of the injected atoms decayed on bone surfaces, we calculate:

$$\frac{1}{10} \times 448 \mu\text{Ci} \times 3.7 \times 10^4 \text{ dis/sec-}\mu\text{Ci} \times 86400 \frac{\text{secs}}{\text{day}} \times \frac{3.62 \text{ days}}{0.693} =$$

$$7.5 \times 10^{11} \text{ disintegrations.}$$

Now 25 nCi ^{224}Ra , steady state, decaying on bone surfaces, will yield, over a thirty-year period:

$$25 \times 10^{-3} \mu\text{Ci} \times 3.7 \times 10^4 \text{ dis/sec-}\mu\text{Ci} \times 86400 \frac{\text{secs}}{\text{day}} \times 365 \frac{\text{days}}{\text{yr}} \times 30 \text{ yrs} =$$

$$8.8 \times 10^{11} \text{ disintegrations.}$$

Thus we see that, to a first approximation, the ^{224}Ra decaying over a thirty-year period on bone surfaces following a 50 ml Thorotrast injection into a standard man, yields about the same number of alpha particles adjacent to bone surfaces as occurred in a patient who developed a bone sarcoma following an injection of ^{224}Ra .

Spiess and Mays⁽¹⁾ calculate the average skeletal dose from injected ^{224}Ra by assuming that each decay yields 25.5 MeV of a energy from ^{224}Ra and its daughters. This assumes 100% of the thoron decays in bone, which may not be the case at all, but since it is our intention to compare our results with the predictions of Spiess and Mays, our dose calculation will be identical to theirs. In the steady state situation, with a constant concentration of 25 nCi ^{224}Ra in a 70 kg man with a 7000 g marrow-free skeleton the average skeletal dose rate is:

$$\begin{aligned}
 \text{Dose rate (rads per year)} &= 365 \frac{\text{days}}{\text{yr}} \times 51.2 \times C \left(\frac{\mu\text{Ci}}{\text{g}} \right) \cdot E \left(\frac{\text{MeV}}{\text{dis}} \right) \text{ rads/day} \\
 &= 365 \times 51.2 \times \frac{25 \times 10^{-3}}{7000} \times 26.5 \\
 &= 1.8 \text{ rads per year.}
 \end{aligned}$$

Similar calculations for a female of 56 kg (the mass used by Spiess and Mays) would yield 2.2 rads per year.

In Table III are listed the average skeletal doses for males (70 kg) and females (50 kg) at each of three injection levels for three different observation times.

TABLE III

Accumulated Skeletal Dose (Rads) from
"Translocatable" ^{224}Ra

Injection Level		Skeletal Dose in Rads		
		20 years	30 years	40 years
Males:	25 ml	18	27	36
	50 ml	36	54	72
	75 ml	54	81	108
Females:	25 ml	22	33	44
	50 ml	44	66	88
	75 ml	66	99	132

It is apparent that these doses are exactly in the region of interest; 20 to 40 years after Thorotrast injections, ^{224}Ra doses range from 20 rads to more than 100 rads. Recalling that ^{224}Ra cases showed sarcomas at 90 rads and above, a large enough population of Thorotrast cases should provide an excellent test of the linear hypothesis at these dose levels.

Table IV shows the expected bone tumor incidence for a population of 1000 cases at each of three injection levels, using the two linear tumor incidence formulations of Spiess and Mays. Specifically, we use their original (I) prediction of 0.90% per 100 rads and also their modified prediction (II) of 1.7% per 100 rads for protracted injection.

TABLE IV

Expected Number of Bone Sarcomas per 1000 Cases

Injection Level		20 years		30 years		40 years	
		I	II	I	II	I	II
Males:	25 ml	1.6	3.1	2.4	4.6	3.2	6.1
	50 ml	3.2	6.1	4.8	9.2	6.4	12.2
	75 ml	4.8	9.2	7.2	13.8	9.6	18.4
Females:	25 ml	2.0	3.7	3.0	5.6	4.0	7.5
	50 ml	4.0	7.5	6.0	11.2	8.0	15.0
	75 ml	6.0	11.2	9.0	16.8	12.0	22.4

Let us apply these predictions to the Portuguese Thorotrast follow-up, as reported by da Silva Horta and da Motta. (6) They have traced more than 1000 cases for about 25 years, state that the average injection was about 25 ml, and report no bone sarcomas. For such a population, assuming equal division between the sexes, we would expect about 4 bone sarcomas from the protracted hypothesis and about 2 bone sarcomas from Spiess and Mays' original hypothesis. The probabilities of seeing none when 4 or 2 are expected out of 1000 cases at risk are 0.018 and 0.135, respectively.

When we consider that a very large number of individuals have been injected with Thorotrast (4300 estimated in the United States by Telles, (7) 10,000 - 100,000 estimated world-wide by Faber (8)), the paucity of documented osteosarcomas is significant. A single case was reported by our group at Argonne; (9) This case was found on the basis of symptoms, and was not a part of any group under study. We know of one case reported in the Japanese literature, (10) and of one case with a fibrosarcoma reported by Zák, *et al.* (11)

The spontaneous primary bone cancer rate in Canada has been estimated to be 6.3 per million population; 58% of these were osteosarcoma, or 3.7 per million per year. (12) At this rate in a population of 10,000 Thorotrast cases, two spontaneous primary bone cancers would be expected over a thirty-year period. It is evident that those seen to date in the various Thorotrast studies fit this expected spontaneous incidence.

Thus, our dose calculations and an assumed linear relation between the skeletal dose from ^{224}Ra and bone sarcoma incidence led us to predict that these sarcomas should be observed in Thorotrast cases, yet they are not. If our assumption of the state of ^{224}Ra in bone is correct, then the linear hypothesis as postulated by Spiess and Mays is not valid at doses below 90 rads, or doses delivered at these low dose rates are not as effective, per rad, as doses delivered at higher dose rates, or both.

This analysis has tacitly assumed that only the alpha particles from ^{224}Ra on bone surfaces contribute to the risk of sarcoma. We know that

^{226}Ra distributed throughout the bone mineral volume is responsible for bone sarcomas in man, so that the alpha particles from ^{228}Th and its daughters in the bone volume, following their creation in ^{228}Ra decay in the bone volume, contribute to the sarcoma risk. Likewise, the alphas from ^{228}Th in bone (probably on bone surfaces) must contribute some effective dose. Thus, considering the contributions ignored in this analysis, the absence of bone tumors is even more surprising.

It is our hypothesis that the paucity of bone sarcomas in Thorotrast cases is a clear indication of a non-linear relationship between dose and effect. For the ^{226}Ra and ^{228}Ra cases, a dose squared relation between dose and tumor incidence has been advanced by Rowland, *et al.* (13) to describe their results. In these cases the dose was delivered continuously, in contrast to the situation in the ^{224}Ra injection cases, where the dose was delivered over a relatively short time period. It may be that the ^{226}Ra and ^{228}Ra cases and the Thorotrast cases, in which the tissues adjacent to bone are subjected to continuous irradiation by alpha particles at very low dose rates, are characterized by a non-linear dose response relationship, whereas the ^{224}Ra injection cases, in which the tissues are irradiated at a much higher dose rate over a relatively short time interval, are characterized by a linear dose response relationship.

The conclusion must be tentative, and await more definitive radiochemical analyses of bone from Thorotrast cases. Nevertheless, it is definite that low alpha doses delivered on bone surfaces at continuous, but very low dose rates, have failed to produce bone tumors in Thorotrast cases, and this may imply that, in man, either there is a non-linear relationship between this dose and bone tumor induction, or a dose rate effect exists for alpha particle irradiation of the tissues adjacent to bone surfaces.

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Chromosome Aberrations Caused by Thorotrast

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Abstract

An attempt to find a dose-effect-relationship between radiation dose (^{224}Ra -equivalent) and chromosome aberration yield (dicentric and accompanying fragments) was made. An increasing statistical correlation was found given by the straight line:

$$y = 6.6 + 0.16 x$$

(y = aberration yield, x = radiation dose)

A computed curve for our values is the power function:

$$y = 4.4 x^{0.22}$$

Although the two relationships are statistically significant (significance level less than 1 %, respectively 5 %) we suggest that it is impossible to establish a dose-effect-relationship between radiation dose and chromosome aberration rate in thorotrast patients, because the number of dicentric scatters within large limits in different patients exposed to equal or similar doses.

Key words:**Thorotrast****Chromosome aberrations****Dose effect relationship****Introduction**

This investigation is part of wider examinations in thorotrast patients made by the German thorotrast study group in Berlin, Heidelberg and Homburg (Saar) (Muth et al. 1971, Muth et al. 1973). In this study we try to obtain a dependence of the chromosome aberration rate from the radiation dose. In irradiated cells many authors found a relationship between radiation dose and number of damaged chromosomes both 'in vitro' and 'in vivo'. PURROT, DOLPHIN et al. (1972) use this relationship as a biological indicator in radiation accidents. However the results of other authors vary so much that it has so far been impossible to use their results as a biological indicator. In this paper it will be discussed if there exists a significant relationship between chromosome aberration ratio and radiation dose as a base for the possible use as a biological indicator. (FISCHER et al. in 1966 reported a significant dose effect relationship in the chromosome aberration rate in 20 thorotrast patients).

Material and Method

68 persons of our thorotrast patients were selected for this investigation. (Because of technical causes no random selection was possible). They had been injected with 3 to 80 ml of thorotrast within the period 1938-1947. The mean exposure time of these patients at the time of the chromosome aberration study was 29 ± 3.7 years.

Lymphocytes of the peripheral blood were cultured in vitro by known methods, used in most laboratories and described in detail in KEMMER et al. 1971. The culturing time including the Colcemid treatment was 48 hours to be sure to find metaphases in first division. Chromosome preparations were analysed by scoring the chromosomes in the metaphase and determining the chromosome aberrations in a phase contrast microscope. All types of chromosome aberrations as terminal and interstitial deletions, multacentrics, dicentrics and rings with or without accompanying fragments were found and scored, but only the dicentric

chromosome aberrations with fragments were used as a measure for the radiation damage.

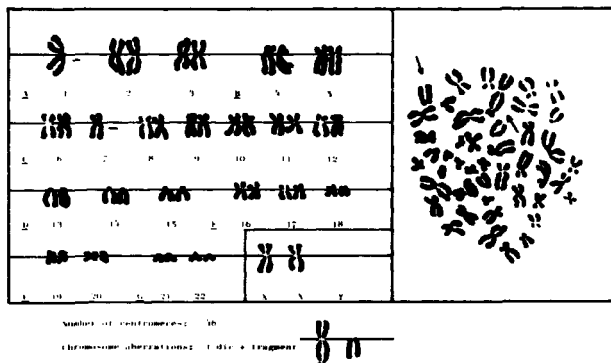


Fig. 1: Radiation induced chromosome aberrations (dic + fragment) in Thorotrast patients.

Control Group

The blood of 70 persons of the same age who had not received any thorotrast injection or appreciable doses of radiation for therapeutic or diagnostic purposes was used for control. These control group is not identical with the control group "B", described in papers of LORENZ et al. 1973 and IMMICH 1973. The results obtained for this control group were in good agreement with published data. In one of the controls did the chromosome aberration rate exceed the natural rate of two breaks per hundred cells. Only 1 dicentric was found in all persons of control group. We therefore assume that the chromosome aberrations found in our patients may indeed be attributed to the radiation effect of thorotrast. This assumption is supported by the fact that the chromosome aberrations found in our study are characteristic for radiation induced chromosome aberrations and not for aberrations induced by other agents.

Chromosome aberrations are only caused by thorotrast stored in the lymphatic system. In patients with perivascular deposits no chromosome aberrations were seen. Therefore we had only to take into consideration the thorotrast activity effective in the RES. In thorotrast patients the thoron (^{220}Rn) arising from the thorium decay series is eliminated in the exhaled air. Using the concentration of thoron measured in the expired air it is possible to calculate the ^{224}Ra -equivalent value (GRILLMAIER 1964). This value is directly proportional to the thorotrast activity in the RES.

Results

Chromosome aberrations were found in all patients with thorotrast deposits. The aberration rate was higher in comparison to the control group. The minimum rate was 1 dicentric/100 cells, the maximum 25 dicentrics/100 cells.

The results are presented in table 1 and figure 2. The ^{224}Ra -equivalent values (abscissa) correspond to the effective radiation dose. (The mean life time of lymphocytes is estimated at approx. 900 days (DOLPHIN 1972) and the exposure time is far more than this time).

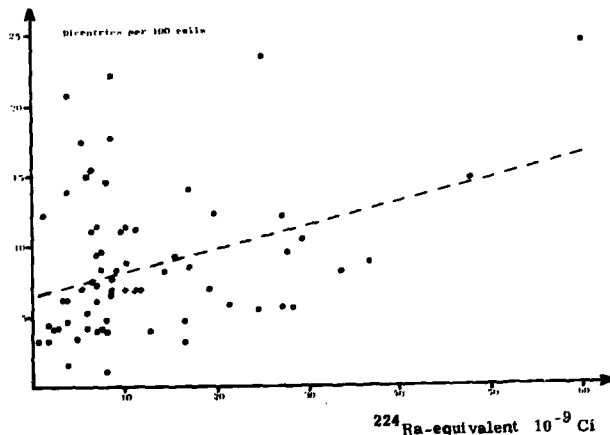


Fig. 2: Dose-effect relationship

Case Nr	Radium equivalent	Dic + per 100 cells		Case Nr	Radium equivalent	Dic + per 100 cells
1	39	3.0		35	8.40	8.4
2	1.20	11.9		36	8.60	17.3
3	1.60	4.2		37	8.60	6.7
4	1.70	3.9		38	8.80	21.7
5	1.80	3.0		39	9.10	8.0
6	3.30	4.0		40	9.70	10.7
7	3.70	1.3		41	10.00	8.5
8	3.75	6.2		42	10.40	11.0
9	3.70	13.5		43	10.50	6.7
10	3.80	6.0		44	11.30	6.6
11	4.10	20.3		45	11.30	11.1
12	4.20	4.4		46	11.60	8.7
13	3.00	2.9		47	12.70	3.7
14	5.20	17.1		48	14.40	8.1
15	6.10	14.6		49	15.60	9.0
16	6.20	5.0		50	16.40	2.8
17	6.20	15.0		51	16.50	2.9
18	6.40	4.0		52	16.70	4.6
19	6.50	10.9		53	16.90	8.3
20	6.70	9.0		54	17.00	13.6
21	6.70	11.0		55	19.30	6.8
22	6.80	5.6		56	19.40	12.0
23	6.90	4.0		57	21.50	5.0
24	6.90	8.7		58	24.40	5.3
25	7.00	4.0		59	24.60	23.6
26	7.10	5.8		60	27.00	5.4
27	7.10	8.9		61	27.20	12.1
28	7.60	9.4		62	27.70	9.3
29	7.60	8.0		63	28.30	5.5
30	7.70	1.0		64	28.90	10.3
31	7.90	4.6		65	33.80	8.2
32	7.90	14.3		66	38.70	8.6
33	7.90	3.8		67	48.10	14.5
34	8.10	7.4		68	60.20	24.0

Table 1 All values used in this investigation

The ordinate shows the dicentric yield per 100 cells. The break rates in relation to the radiation dose vary for different patients within wide limits.

In seeking a statistical correlation of the relationship between the chromosome aberration rate and the radiation exposure the large scattering of the values allowed only to assume that this relationship should be a linear equation, although other types of functional relationship could not be excluded. The regression straight line found is given by the fol-

lowing function:

$$y = 6.6 + 0.16 x$$

Correlation coefficient 0.3352

Significance level 1 %

(y = aberration yield,
x = radiation dose)

However, the real relationship cannot be a straight line because - apart from fundamental considerations - the regression straight line found does not cut the ordinate at the zero point. At dose 0 the aberration rate must be that of the controls. It was therefore suggested that an estimated curve for the dose-effect relationship is a power function of the following type as widely used in investigations concerning radiation induced chromosome aberrations:

$$y = k \cdot x^n$$

The computed relationship is:

$$y = 4.4 x^{0.22}$$

Correlation coefficient 0.2996

Significance level 5 %

(y = aberration yield,
k = constant,
x = dose)

Discussion

It is obvious, that these results do not allow to use this method as a biological indicator for the radiation dose or damage, because the aberration yield of patients with similar thorotrast amounts formerly injected varies within large limits. Besides it is surprising that the power exponent in the computed dose-effect relationship is less than 1, while in "in vitro" and in other "in vivo" experiments it is between 1 and 2 (MOURIQUAND et al. 1971). There are many possibilities to explain these results:

1. It is possible that "in vivo" damaged cells are eliminated by the body.
2. The thorotrast-deposits in the RES are differently conglomerate (KAUL 1969, 1973, v. KAICK et al. 1973). Therefore the self-absorption of the alpha-particles varies with the size of the thoro-

trast conglomerations, so that the effective radiation dose and the radiation damage may be different in patients with the same thorotrast amounts in the RES. The effective radiation dose damaging the lymphocytes must therefore not be proportional to the amount of thorotrast formerly injected. The estimation of the elimination rate of thoron from Thorotrast deposits with different conglomerations is difficult.

3. The variance of the results may be due to changes in the ratio of aberrant to normal cells in the lymphocyte pool, or changes in the relationship between the blood lymphocyte pool and the body lymphocyte pool. Examinations periodically made in two thorotrast patients show a variance in the dicentric aberration yield (Table 2).

Patient W.		Patient Seb.	
lower dose $1.5 \cdot 10^{-3}$ Ci (^{224}Ra - equivalent)		higher dose $15.3 \cdot 10^{-3}$ Ci (^{224}Ra - equivalent)	
date of investigation month/year	Dic. + / 100 cells	date of investigation month/year	Dic. + / 100 cells
05.70	2	11.70	8.6
06.70	1	03.71	7.7
06.70	-	07.71	5.2
08.70	-	08.71	9.4

Table 2 Dicentric yield in patients with different Thorotrast burdens

4. In all Thorotrast patients relative high deposits of Thorotrast were found in lymph nodes independent on the total RES burden. That means that the effective radiation exposure of lymphocytes is quite the same. This fact may explain that the chromosome damage in patients with lower amounts of Thorotrast injected is relatively high. (Fig. 3.)

To be sure that our results are not impaired by errors of method we checked the method by irradiating lymphocyte cultures "in vitro".

The results obtained are in good agreement with those reported by other authors. Examinations in patients treated with radiolodine also gave results with good dose-effect relationships.

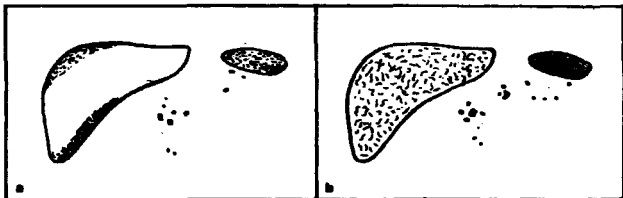


Fig. 3: Thorotrast deposits in the RES in patients with lower (a) and higher (b) Thorotrast amounts formerly injected

Conclusions

In the present status we suggest that it is very difficult probably impossible to establish a dose effect relationship between radiation dose and chromosome aberration yield in thorotrast patients. The aberration yield cannot be used as a biological indicator for the radiation dose.

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The Edinburgh Thorotrast Series - Report of a Cytogenetic Study

by

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Introduction

The purpose of this paper is to present the data derived from the study of cytogenetic damage in the peripheral blood leukocytes of persons who had received intra arterial injections of 232-thorium dioxide in the past.

The study population was defined by the identification in the records, relating to the years 1926-1955 inclusive, in the Department of Surgical Neurology, Edinburgh, of 142 patients who had received Thorotrast in the course of cerebral angiography. Twenty-two of these patients died within one year of the injection, as a direct result of the disease for which they were investigated, and a further ten patients with permanent foreign residence (current status unknown) were excluded from the study. There remained therefore 110 patients, comprising 54 men and 56 women, in the study population.

Results

All 110 patients were successfully traced and information on the morbidity and mortality subsequent to the intra arterial injection of Thorotrast/

Thorotrast obtained by interview, from the replies from doctors to questionnaires and from the examination of hospital records relating to subsequent hospital admissions.

By December 31st, 1972, 60 deaths had been notified and the distribution of these deaths between malignant and non-malignant causes is shown in Table I, together with data relating to the volume of Thorotrast injected.

A detailed report of the long term hazards in this group of patients has already been published (Boyd et al., 1968). Since that report a further four liver tumours have been notified to us so that 8 of the 18 deaths due to cancer were due to a primary tumour of the liver. These 8 liver tumours comprised 5 cholangiocarcinomas, 2 hepatocellular carcinomas and 1 haemangi endothelioma. The tumours occurred between 19 and 37 years after injection (mean 27 years); the patients having received between 14 and 78 ml Thorotrast (mean 32 ml).

Since the 1968 report (Boyd et al., 1968) which included a death from aplastic anaemia and one from giant follicular lymphoma, a further death from a blood dyscrasia has occurred. The patient, a man, died from acute leukaemia 22 years after receiving 30 ml of Thorotrast.

Cytogenetic Studies

When/

When peripheral blood is grown in culture with phytohaemagglutinin the small lymphocyte can be induced to enlarge to form a blast cell and divide. If the cell is arrested in the metaphase stage of the division then the chromosomes in the cells can be examined. It has been found that the chromosomes in the small lymphocytes of persons who have been exposed to irradiation show chromosome aberrations. The number of dicentric/ring aberrations in blood cells of persons exposed to known doses of external radiation is proportional to the dose received, and therefore the frequency of these aberrations can be used for dosimetry (UNSCEAR 1969). It was hoped that it would be possible to use chromosome damage in the small lymphocyte as a dosimeter also for internal emitters, especially for irradiation received from Thorotrast where the dose to the individual injected is very difficult to assess.

Fischer et al (1966) found that there was a positive correlation between the body burden of thorium in Thorotrast patients and the number of chromosome breakage events in their small lymphocytes. However this was only a correlation and the points on the graph are widely dispersed.

In our original examination (Buckton et al, 1967) of the chromosome aberration frequency in 36 patients 33 of whom had been injected with known amounts of Thorotrast, we could find no significant relationship between chromosome aberration frequency and dose, when dose was/

was expressed as the product of 'mls of Thorotrast injected' and years since injection. It may have been that this was not a very good estimate of dose, but Hemphill and Hasselgren (1971) have reported that mls of Thorotrast injected gave a satisfactory estimate of body burden.

Re-examination of our early data, together with additional new data on a further 8 patients indicates that there is some association between chromosome aberrations and the volume of Thorotrast injected. In this analysis the chromosome aberration data has been expressed in terms of the minimum number of chromosome breaks that would have been required to take place to produce the aberrations seen (e. g. one break for a deletion, 2 breaks for an interchange etc.). The association found between the estimated number of chromosome breaks and mls of Thorotrast injected had a correlation coefficient of 0.3121 and was significant at the 5% level. When the number of chromosome breaks in 100 cells from 41 patients was plotted against mls of Thorotrast injected ^{multiplied} / by the years since administration (Fig. 1) the correlation coefficient was 0.3008 and was significant at the 10% level. The regression line shown in the figure was found to be given by the equation. $\text{Breaks} = 33.47 + 0.028 (\text{mls of Thorotrast} \times \text{time since administration})$. The vertical line shows the confidence limits which are wide, and leaves no doubt that, in this situation, chromosome break frequencies are not a good parameter for dosimetry. This result/

result is not surprising, for the distribution of the thorium in the organs of the body after administration varies between patients and in some patients the thorium is largely retained in perivascular sites. Moreover, the method of weighting aberrations to give break frequencies is open to objection since at least some of the simple deletions are a consequence of two and not one break.

In order to obtain a better estimate of the body burdens in our patients, 14 were submitted to whole body counting. This was performed by a linear scan of the whole body measuring the γ -ray emission, which was then calculated as nannocuries of thorium ²²⁸. Table II shows the whole body counts for the 14 patients by increasing body burden. The cytogenetic results for peripheral blood sampled on the same day as the whole body counting are also given. The cytogenetic results in Table II are expressed as:-

- 1) Total number of unstable cells, i. e. cells with dicentric or ring chromosomes or acentric fragments.
- 2) Numbers of dicentric and ring chromosomes, since these are the most characteristic and most easily identified aberrations induced by irradiation.
- 3) Total number of stable cells, i. e. cells with abnormal monocentric chromosomes, although not easily identified, these cells are likely to be fully viable.
- 4)/

4) Total chromosome breaks, i. e. the minimum number of breaks in the chromosomes that would be required for the aberrations seen to be formed.

Comparison of the whole body count with the cytogenetic results shows no direct relationship with any of the parameters. On 13 of these patients a cytogenetic analysis had been done 3 to 4 years previously and it is interesting to note that there has been very little change in the aberration frequencies in these patients in that time. It would appear therefore that the relative number of damaged cells over this period of time after Thorotrast injection remains relatively constant.

We have examined the chromosomes of a total of 59 of the patients in the Edinburgh Thorotrast series, among these patients we have found 3 who have a clone of cells marked by a stable rearrangement of the chromosomes. The finding of a lymphocyte clone in an individual is a very rare event (Court Brown, 1967), therefore these clones in the Thorotrast patients are of considerable interest. Two of these cases have been described previously (Buckton et al., 1967).

1) Case 19 in the previous report received 18 mls of Thorotrast during right carotid angiography at the age of 48. Thirty-one years later, when chromosome studies were done, he was found to have a clone/

clone of abnormal cells marked by four rearranged chromosomes. This patient was suffering from a blood dyscrasia at the time of the cytogenetic examination from which he died shortly afterwards. On post mortem examination he was found to have Ca Lung.

2) Case 10 in the previous report also received 18 mls of Thorotrast during right carotid angiography at the age of 49. Chromosome analysis twenty-two years later revealed that he had a clone marked by one abnormal No. 3 chromosome. In subsequent cytogenetic analysis the number of these clone cells has been variable as can be seen from Table III. There are no further chromosome studies on this patient as he developed a Ca. Bladder, for which he was treated with radiotherapy. He was alive on the 31st December 1972.

3) Case 6 in the previous report received 17 mls of Thorotrast for right carotid angiography at the age of 37. On the first cytogenetic analysis twenty-one years later he was found to have two cells with 4 abnormal chromosomes but this was not felt to be sufficient evidence for a clone. However, on chromosome analysis 4 years later eleven of the 100 cells analysed were found to have the same 4 abnormal chromosomes which were later identified with fluorescence as chromosomes 12, 14, 15 and 22 (Clone I). Also 3 more cells had another chromosomal rearrangement also involving 4 chromosomes which were later identified by fluorescence as both No. 6 chromosomes, chromosome/

chromosome 7 and 22 (Clone II). Since 1966 we have made repeated observations on this man. The frequency of the two clones in the peripheral blood lymphocytes is shown in Table IV, the numbers vary with time but the clone cells do not appear to be increasing significantly since 1970. This patient remains well.

Although cytogenetic analysis of the peripheral blood of Thorotrast patients has not proved useful for dosimetry, it is a useful guide to the level of biological damage present in the reticulo endothelial system. Where there is a high number of cells with stable rearrangements there would appear to be a high probability of finding a clone of cells with rearranged chromosomes. The clinical significance of these clones is unknown. They may provide an early indication of the development of malignancy, however this remains to be demonstrated. Further cytogenetic analyses of Thorotrast patients is certainly required.

Acknowledgements

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assistance and much of the chromosome analysis.

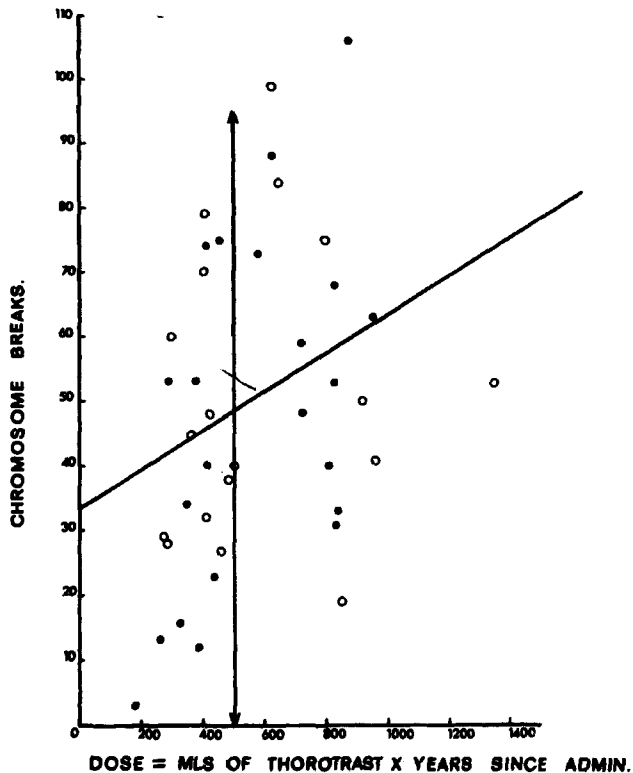
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CORRELATION BETWEEN CHROMOSOME BREAKS AND DOSE.

Female = 0

Male = ●



**TABLE III: NUMBERS OF CLONE CELLS IN A
THOROTRAST PATIENT GIVEN 18 ccs IN THE R.I.C. ON 26.1.44**

Date of Culture	Total Cells Analysed	Total Unstable Cells	Total Stable Cells	No. of Clone Cells
6.6.66	200	19	21	4
15.9.66	200	14	15	0
10.3.67	200	24	29	7
13.1.70	100	9	16	0

**TABLE IV: NUMBERS OF CLONE CELLS IN A
THOROTRAST PATIENT GIVEN 17 ccs IN THE R.I.C. ON 31.1.45**

Date of Culture	Total Cells Analysed	Total Unstable Cells	Total Stable Cells	No. of Clone I Cells	No. of Clone II Cells
24.10.66	100	9	10	2	0
14.7.70	100	6	19	11	3
12.10.70	200	6	61	23	15
30.11.70	100	4	30	12	7
8.2.71	100	5	26	7	5
5.4.71	100	9	17	5	3
31.5.71	100	1	22	12	6
26.7.71	100	5	16	2	1
15.11.71	100	3	25	8	7

Followup of Thorotrast Patients from Boston, Massachusetts
and Ann Arbor, Michigan, USA

by

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Abstract

724 patients who received Thorotrast for cerebral angiography and 315 control patients who underwent similar examinations were followed up to determine the incidence of radiation related morbidity and mortality. 42 of the Thorotrast patients and 29 of the controls were subjected to extensive clinical and laboratory examinations. In the Thorotrast series, one case each of liver tumor, granulocytic leukemia, and non-alcoholic hepatic cirrhosis were found as well as two cases of localized thorotrastomas. The Thorotrast patients revealed evidence of early liver dysfunction by elevations in bromsulphalein retention and alkaline phosphatase tests. The most sensitive indicator of radiation exposure was the high frequency of chromosome aberrations. Anemia, elevated white counts, and abnormalities in red cell morphology were not found.

Followup of Thorotrast Patients from Boston, Massachusetts
and Ann Arbor, Michigan, USA

INTRODUCTION

Thorotrast did not receive the wide utilization in the United States that it did in many other countries in the world. An estimate⁽¹⁾ that less than 5000 patients received this contrast material does not seem unreasonable. Major concentrations of cases were located in Minnesota, New York, Pennsylvania, Michigan, Washington, D.C., and Massachusetts among others. No formal attempt has ever been made to organize a nationwide study in our country, and the status of most of the patients is entirely unknown. We were able to assemble a roster of over 700 patients who received Thorotrast for cerebral angiography and over 300 control patients who underwent similar examinations with a non-radioactive medium (Diodrast). This work was performed between 1964 and 1970 and has been reported previously.^(2,3,4)

METHODS

Only patients who had undergone cerebral arteriography were selected for the study because of the lack of any known relationship between central nervous system disease and malignancy elsewhere. The control series consisted of patients who had undergone cerebral arteriography in which a non-radioactive contrast material was used during time period of Thorotrast administration. At the

Massachusetts General Hospital^(MGH), cerebral arteriography was performed in the operating room using an arterial cutdown technique under general anesthesia. A roster of 200 patients who underwent Thorotrast arteriography and a control roster of 134 patients were assembled from the operating room log books. At the Lahey Clinic^(LC), a roster consisting of 175 Thorotrast arteriographic patients and 181 control patients was assembled from the medical record department. At the University of Michigan^(UM), a roster of 349 patients who had undergone Thorotrast arteriography was assembled from the records of the radiology department; no control series was selected at this institution.

The patient's original hospital chart was abstracted to ascertain his general health status as determined by the clinical impression and by pertinent laboratory tests performed during the arteriogram admission. In addition to the dose of Thorotrast, the patient's age, sex, and pertinent identifying information were also recorded. In instances of death, a copy of the death certificate was obtained to determine the cause of death. In living patients, the followup consisted of completion of a questionnaire dealing with the patient's current and past illnesses. This information was obtained by telephone and by mail. All information was verified

by contacting the family physician identified by the patient or by obtaining copies of the patient's previous hospital record.

42 of the Thorotrast group and 29 of the control patients from the MGH were subjected to physical and laboratory examinations. Many of these patients were examined twice within a three or four year period. The physical examination was a standardized one with particular attention paid to signs of liver dysfunction or development of malignant tumors. Laboratory examinations included

extensive tests of liver function tests (bilirubin, bromsulphalein retention, serum glutamic oxaloacetic transaminase, alkaline phosphatase, prothrombin time, thymol turbidity, cephalin flocculation, total protein and serum electrophoresis). A complete blood count including differential and red blood cell morphological analysis as well as chromosome analysis were performed. X-ray films of the entire body were obtained. The patients exposed to Thorotrast underwent whole body counting in order to measure their body burdens of radioactivity. The control patients underwent similar examinations excluding whole body counting. No patients from the LC or UM were examined.

ADMISSION CHARACTERISTICS

The most common indication for cerebral arteriography were the expected ones: namely, aneurysm, subarachnoid hemorrhage, and tumor. Approximately 40% of the patients

underwent arteriography for a variety of other conditions including seizures, vascular disease and headache. The indications for arteriography for the control series was similar to those of the Thorotrast patients. The median dose of Thorotrast administered at all centers was 24 cc., being 28 cc. at the MGH, 12 cc. at the LC and 30 cc. at the UM.

The median age of both the Thorotrast and control patients at all centers was 44 years and the patients were approximately evenly distributed between males and females. Of the patients receiving Thorotrast approximately 72% did so prior to 1949. The cause of death was related to the presenting neurological disease in 70% of the patients; approximately 5% of the patients died of non-central nervous system malignant tumors.

FOLLOWUP

At the MGH it was possible to locate 199 of the 200 Thorotrast patients. Of these, 70 were living while 129 were deceased. All but 9 of the controls were located. At the LC 167 of the 175 Thorotrast patients and 172 of the 181 control patients were located. The numbers living were 69 and 80, respectively. At the UM 310 of the 349 cases were studied; 71 were alive and 239 were dead. The mean duration of followup for the living Thorotrast patients was 22 years and the maximum periods of followup were 24, 27, and 28 years at the MGH, LC and UM, respectively. Of the living Thorotrast

patients, 60% at the MGH, 98% at the LC and 91% of the UM, were followed for at least 20 years. Total person years among the Thorotrast patients was 7249 years as compared to 3720 years among the controls. The remaining characteristics of the controls were similar to the Thorotrast group.

RESULTS OF THE CLINICAL FOLLOWUP

37 malignant tumors were detected in the Thorotrast patients, and 13 in the control series; taking person-years into account, there was no increased incidence in either group. In regards to the usual Thorotrast associated malignancies, one case of liver cancer occurred in both the Thorotrast and control series. Three cases of leukemia occurred in the Thorotrast series, only one of which was granulocytic in type. Three cases of lung cancer occurred in the Thorotrast series and two in the control series while no bone tumors were found. Of non-neoplastic Thorotrast attributable disease, there was one presumed non-alcoholic cirrhosis in the Thorotrast patients and two cases of thoratrastomas. No cases of aplastic anemia were found.

RESULTS OF LABORATORY EXAMINATIONS

The techniques used in the examination of the patients have been given elsewhere⁽³⁾ and will not be repeated in detail here. X-ray films revealed the typical pattern of deposition of Thorotrast in the liver, spleen and periportal lymph nodes. No relationship was apparent

between the size and density of these organs and the amount of Thorotrast administered. Films of the bones failed to reveal evidence of alteration in bony trabecular pattern.

37 of the 42 Thorotrast patients underwent whole body counting using the meter-arc technique with an 11 X 4 inch sodium iodide crystal connected to a 400 channel analyser. The gram equivalents of ^{232}Th were calculated and were shown to closely correlate with the amount of Thorotrast originally administered. The whole body burdens ranged from 0.42 to 2.51 gram equivalents of ^{232}Th , with an administered dose of 30 cc resulting in a body burden of between 1.0 and 1.5 gram equivalents.

Slightly more than 40% of the Thorotrast patients revealed evidence of early liver dysfunction as indicated by elevations in the bromsulphalein retention (greater than 10%) and alkaline phosphatase (greater than 5 units) tests. A dose-response was not evident in relating Thorotrast-years or calculated liver dose in rads to these abnormal liver function tests.

Chromosome analysis on peripheral lymphocytes was performed using a modification of the method of Moorhead et al⁽⁵⁾. The blood was obtained before x-ray examination and cultured for 48 hours. The metaphase nuclei of 50 cells were counted in 25 cases. A ring, dicentric, or rearrangement was counted as two

breaks each and a fragment as one break. There was a striking excess of breaks among the Thorotrast cases with a median of 34 and a range of 0-113. The control series did not reveal such changes. There was no indication of a dose-response relationship.

All other laboratory studies failed to show significant differences between the cases and control series. In general, the laboratory tests in the controls were unremarkable. Specifically, there was no evidence of abnormality of the erythrocyte morphology, no anemia, and no elevation of white cell count.

DISCUSSION

The present study has several unique features including the use of a control group as well as the results of rather extensive physical and laboratory examination of 41 of the living Thorotrast patients.

The relatively low incidence of malignancy in the series⁽⁶⁾ (one hemangioendothelioma, one granulocytic leukemia,) may be partially explained by the relatively small doses of Thorotrast used as well as the short followup period. Previous reports have suggested that liver tumors are more prone to develop in patients who received more than 40 cc. of Thorotrast⁽⁷⁾ in which a time period of more than 30 years had lapsed⁽⁸⁾ since the administration of the Thorotrast.

In the relatively extensive set of clinical and laboratory tests, apparent effects of Thorotrast were

seen in the bromsulphalein and serum alkaline phosphatase tests which showed evidence of early liver dysfunction in about one half of the patients. The best indicator of Thorotrast exposure was the aberrations in the chromosomes⁽⁹⁾. Although there has been a previous suggestion that these abnormalities are dose dependent⁽¹⁰⁾ we were unable to confirm such a relationship. Our failure to find abnormalities in red cell morphology⁽¹¹⁾ and our lack of cases of anemia⁽¹²⁾ is also of interest.

In the course of the study, three possible Thorotrast attributable deaths from cases not in our series were uncovered. These included one case of cholangiohepatoma, a hepatoma and a case of aplastic anemia, respectively. Pertinent demographic data was not available for these cases.

The Thorotrast patients represent an unreplaceable potential source of information on the long term effects of chronic radiation in humans. It is unfortunate that the lack of government funds has temporarily signed the death knell of continuation of the present study or of future studies in this area in the United States.

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Follow-up of danish Thorotrast cases.

by

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The temporary results of the follow-up of 1.005 Thorotrast injected patients are presented. Among the 756 patients who did not die from the neurosurgical disease 312 have died. 28 died from hepatic tumors of which 11 were the typical Thorotrast induced haemangioendotheliomas all with a latency period above 15 years. A further 11 died from leucemia with latency period as low as 7 - 8 years. The expected rate of death from all these tumors is less than 5. The follow-up continues.

In long term studies like the present epidemiological follow-up of Thorotrast injected patients it is necessary with intervals to make a complete inventory on the state and correlations in the observations collected. Only in this way will it be possible to find the actual points of interest and to register the new developments taking place in the group under observation.

The preparation Thorotrast was used in Denmark from 1935 until 1947 and the follow-up of the group was started at the Finsenlaboraty in 1949.

The follow-up has been laborious and only during recent years has it become absolutely evident how important the follow up has been. Due to a massive underestimation of both size and type of effect and of latency periode between injection and induced malignant tumors the project was started as an acute study - while it is now quite evident that it will be my successor at the Finsenlaboratory who will conclude the study.

The patients had all been admitted to the two neurosurgical departments in Denmark and had during their stay here been examined with an intravenous carotid angiography.

A thorough search through the case histories of these departments has disclosed 1.005 patients where colloid Thorium dioxide was injected. A further number of cases is known who are not included but who might have been injected. They have had an arteriography performed at the time when iodine compounds again were becoming available, but there is no note in

the case history of what contrast medium has been used.

Both groups are subject to a continuous follow up, primarily by a control of all Danish death certificates but combined with a periodical verification of the status of those known to be alive. The radioactivity and the amount of Thorotrast has only been measured in a small number of patients. In most of the dead the presence of Thorotrast has been verified through autopsy, at hospital admissions or by radiography. Otherwise the information from the case histories has been considered valid. The distribution of the patients according to sex and time of injection can be seen from Table I.

The amount of Thorium dioxide injected varied as seen in Table II.

During the first years after the injection a number of the patients died from the neurosurgical disease, for which the arteriography was performed. This group shall not be considered further. The rest of the patients have since 1949 shown a constant yearly mortality from all causes. (Fig.I). The rate of death has for the males been 7,6 persons per year and for the females 4,0 per year. If this rate of death continues until the disappearance of the group, this will require a further observation of 30 years for the males and 57,5 years for the females. At time of the last death, the age of the youngest surviving person should be 65 years for the male and 87 years for the female. The calculation may thus be reasonable.

The main causes of death are the ones expected from a

mixed group with an age distribution as the present one, and with cardiovascular diseases as the most common one. A relative large number of suicides and accidents is observed, but this must in all probability be due to the underlying reason for hospital admission, head aches and epilepsia. Only two groups of non-malignant diseases shall be mentioned. Among the dead are found 8 cases where hepatic cirrhosis has been the cause of death. As the occurrence of this disease is not registered in this country the incidence in relation to the expected can not be evaluated. It is however interesting that the number of cases appear to be increasing with time. Of the 8 only 3 died less than 25 years after the Thorotrast injection. The other 5 appeared later, up to 31 years after the injection. This could support the possibility of a dependency of the cirrhosis on the Thorotrast.

The other set of diseases are the non-leucemic haematological diseases. The number of cases with these diseases were increased above the expected in the ABCU studies in Japan (1,2). In the present material there has however been no increase during recent years in the number of these cases - the five previously published (3) are still the only ones known.

The greatest interest is however centered on the incidence of all types of cancers in the material. In Fig. II is seen the year by year cumulative rise in verified cancers, dead or diagnosed, in relation to the expected incidence for a group of persons with identical age and sex as calculated from the

Danish cancer register data corrected for the expected incidence of brain tumors. As the presence of such a tumor could be the reason for entrance into the material it was deleted in this estimate.

It can be seen that the males for a number of years have shown an increase above the expected. This increase which has been growing year by year. The incidence for the females stayed for some years below the expected curve, but during recent years this group has also risen above the expected.

The localization of the malignant tumors and the leucemias is given in Table III together with estimates of the expected incidence calculated on the basis of the cancer register data. It will be evident that two tumor localizations are of main interest, the tumors of the liver and the leucemias.

As far as the other tumors are concerned the observed incidence is well below the expected in practically all cases. Only the pulmonary cancer will give rise to special comments. As we heard there is a continuous excretion of Thoron in the breath, and significant dose to the bronchi can be calculated. In the present material the overall incidence is 8 cases with 4 expected which could fit a radiation carcinogenesis. It is however significant that although 0,5 cases were expected among the females none are seen. If Thorium through Thoron should represent a carcinogenic hazard in itself an identical increase of 2 tumor cases should have been observed in both sexes. As this is not the case it would be prudent to reserve the judgement on the Thorium dependancy of these tumors, at

least on the basis of this material. It is interesting that the Portuguese investigators have taken the same position, although for a somewhat different reason (4).

Two main groups of liver tumors are found; the haemangio-endotheliomas and the more common hepatocholangio carcinomas.

The first mentioned tumor has repeatedly been shown both in human experiences (5) and in animal experiments (6) to be a type of tumor intimately connected with Thorotrast deposits in the liver in man and in the spleen in some animals like the rabbit.

In order to evaluate the carcinogenesis in the liver tumors and the leucemias a knowledge of the pattern of appearance in relation to the time after Thorotrast injection is necessary. If there is a difference in the provoking mechanism among the Thorotrast tumors themselves or in comparison with the other tumors found in the Thorotrast patients this could be evident from the pattern of appearance with time. (Fig.3).

The cumulative incidence of those tumors where no causal relation to the Thorotrast is suspected rises by a straight line starting immediately after the injection.

The Thorotrast induced tumors however show quite a different pattern. The curve shows a latency period without any tumor and this latency period varies among the different malignancies.

As was to be expected the leucemias have the shortest latency period of not more than 5 - 7 years. The curve for the

rise in cumulative number follows reasonably close to a straight line although a semilogarithmic plot may give a more straight line.

The curve for the liver carcinomas and the one for the haemangioendotheliomas have latency periods close to 15 years. Both rise reasonably rectilinear with time and it is doubtful whether these two curves can be considered different. The slope of the curve for the haemangioendotheliomas is not too significant due to the small number of cases.

It is difficult to compare the observed incidence between the groups of patients followed in different countries, it can however be mentioned that the rate of appearance and the latency period for the haemangiomas is practically the same in the Danish and in the Portuguese material which is of approximately the same size (Fig.4).

In the evaluation of these curves a certain unreliability has to be recognised. As of January 1973 it is 38 years since the first patient was injected with Thorotrast. It is however only 27 years since this happened to the last one. This means that only that part of the curves in Fig. 3 which covers the first 27 years after the injection represents completed observations. During the next years more cases will probably appear, and they may change the last part of the curve.

It is interesting that no cases of leucemia have appeared later than 23 years after the injection, and that the same is the case with the non-leucemic haematological diseases. This

may be a sign that the spatial distribution of the irradiation to the bone marrow has become such that no radiation is received by the sensitive cells. This is not very probable and the significance of this observation can as far as the Thorotrast patients are concerned not be resolved from this material alone.

This presentation of the factual information obtained by close to 25 years of follow up of this group of patients must lead to the conclusion that an increase in leucemias and in certain liver tumors has been observed. Out of some 250 dead 28 have died from Thorotrast induced liver tumors and 10 of leucemia and they show no sign so far of a decrease in rate of appearance. On the other hand no new tumors which can be ascribed to Thorotrast have been found from this survey.

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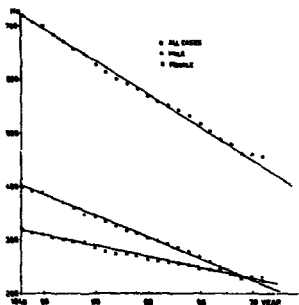


Fig. I.

The year by year decrease in surviving patients.

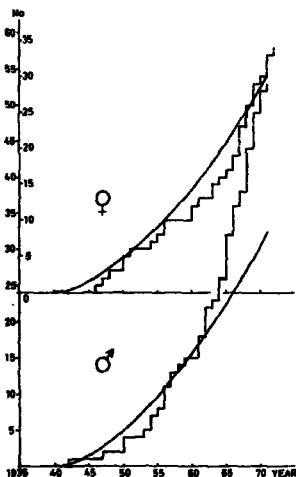


Fig. II.

The cumulative incidence of malignant tumors and leucemias compared to the expected calculated from Danish Cancer Register data after exclusion of brain tumors and taking the actual age and sex into consideration.

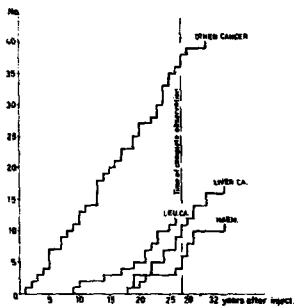


Fig. III.

The cumulative incidence of tumors and leucemias according to year after injection.

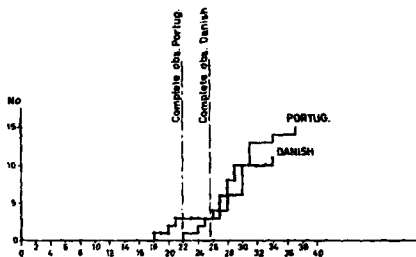


Fig. IV.

Comparison of Danish and Portuguese
haemangioendotheliomas,

Table I.

Thorotrast patients according to year of injection, sex and type of death.

Year of inj.	Sex	Total material	Dead from neurosurg. disease	Material proper	Dead	Living	Living
		No.	No.	No.	No.	No.	%
1935-38	M	51	11	40	22	18	45
	F	43	7	36	18	18	50
1939-41	M	133	18	115	58	57	50
	F	84	10	74	36	38	51
1942-44	M	203	62	141	55	86	61
	F	143	42	101	22	79	78
1945-46	M	178	61	117	53	64	55
	F	170	38	132	48	84	64
TOTAL		1.005	249	756	312	444	

Table II.

Relative distribution of injected dose of Thorium dioxide solution.

Injected at	All cases		Thorotrast tumors and leucemias		Other tumors	
	%	mean	%	mean	%	mean
5-9	1		0		2	
10-19	43	76	22	43	41	70
20-29	32		21		27	
30-39	8		16		7	
40-49	5	16	8	38	5	15
50	3		14		3	
unknown	8		19		15	

Table III.

Observed and expected cancer by region.

	Males		Females		All	
	observed	expected	observed	expected	observed	expected
Gastro-intest.	8	12,9	5	8,2	13	27,1
Primary liver	10	0,38	7	0,25	17	0,63
Haemangio.	7	0	4	0	11	0
Pulm.	8	3,5	0	0,5	8	4,0
Pleurae	3	<0,02	0	<0,02	3	<0,04
Breast	0		2	6	2	6
Female genit.	0		6	7,6	6	7,6
Male genit.	2	3,5	0		2	3,5
Leuc.	6	2,7	5	2,0	11	4,7
Other haematol.	2		1		3	
Others	5		4		9	
	50	(32)	33		83	

Statistical Problems of Thorotrast Studies

by

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Abstract

A cross-section study on the toxicity of thorotrast demands a control-group. The postulates in order to establish a control-group are discussed. Evaluation of data will be performed for the first time as soon as the collection of the whole universe under study has been terminated.

Introduction

This paper should like to inform you on various ideas which have effected us during the planning period of the German thorotrast study.

The Main Question

The Analyst has to answer the question: Given any pathological finding in members of the carrier-group. Has this finding been produced by the toxicity of thorotrast or not? E.G.: Under onehundred male thorotrast carriers you will find three patients suffering from a carcinoma of the prostate. Are these carcinomas caused by thorotrast or not? The question leads to the hypothesis:

The coincidence of thorotrast-administration 35 years ago and the present carcinoma of prostate has been produced by chance only.

Then the analyst has to decide, whether the hypothesis has to be rejected or not. This is possible by means of a con-

trol-group only. That is the reason why the main problem in the present German study runs as follows:

How to establish a Control-group?

With sufficient energy it is relative easy to find a large group of thorotrast carriers. However, it is a very difficult task, to define a control-group, because the following postulates must be fulfilled:

- (i) The borderline between the two groups must be defined
- (ii) The groups must be comparable with regard to time
- (iii) The groups must be comparable concerning age and sex (or race, if necessary)
- (iv) The intensitiy of physical, radiological and laboratory examination must be equal.

Ad (i): The first postulate demands mature consideration. It seems to be the simplest manner, to compare the thorotrast-carriers with patients, who have received another contrast-injection. However, this method is not practicable, because in 1935 through 1941 all patients requiring a contrast-injection have received thorotrast without any exception, at least in Germany. That is the reason why we have defined the borderline as follows: Patients, who did receive thorotrast versus patients, who did not receive thorotrast, without respect of the underlying disease.

Ad (ii): The so called historical comparison is a very bad one, because you will get a doubtful conclusion in every case: If you detect any distinction between the carriers and the control-group, you cannot decide, whether the distinction is true or produced by the lag of time between the hospitalisation of the carriers and the hospitalisation of the control-group. That is the reason why we collect the control-group out of the no-thorotrast-patients of the same time (1935 through 1941) and the same hospital.

Ad (iii): The method of matched pairs is the most common one to fulfill the third postulate. However, the structure of the control-group is predetermined by the structure of the carrier-group. Neither the carrier-group is collected randomly

nor the control-group. That is the reason why in the German study the control-group has been drawn according to the B as the first letter of the surname. This method is a pseudo-random one. For evaluation reasons subsamples according to age and sex are provided both from the carrier- and the control-group.

Ad (iv): The way of obtaining catamnestic data as well as the physical, radiological and laboratory examination of the still living patients under study is standardized. The related data sheets are standardized also.

Evaluation of a Cross-section Study

The collection of a sufficient large sample both of carriers and of control-patients is a time consuming process. If you wish to evaluate the data of the already collected patients stepwise, e.g. yearly, then the independency of data is not guaranteed. F.i.: The first one hundred patients evaluated after the first year are included in the 250 patients evaluated after the second year and so on. This way enables you to reject the hypothesis very early, only by the lack of independency, and not because a true difference between the carrier- and the control-group. That is the reason why the evaluation of data cannot be performed till then the collection of all patients under study has been terminated.

Development and Improvement of the Questionnaires

by

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Two points of view are decisive for the documentation of the data occurring in the Thorotrast-research project: 1. Complete acquisition of all important data, as far as possible, and 2. suitable coding with a view to the statistical evaluation by the computer.

For the data acquisition we chose questionnaires containing on the left side the corresponding questions which are to be answered on the right side either coded or in free text. The coded information of one questionnaire can be transferred to one punched card.

In its present form the data set comprises a total of 5 questionnaires: the so-called medical record questionnaire, three clinical questionnaires and a final questionnaire for deceased or lost patients.

The data processing is divided into the following parts:

1. The collection of medical record data. It consists in transferring the essential data from the patient hospital record to the medical record questionnaire. The information thus acquired consists, above all, of personal data, administrative information, diagnoses and information on possible thorotrast application.
2. The examination of the patient. It begins with the case history which is recorded on the clinical questionnaire I. This includes several questions referring to the time prior to the thorotrast injection. The results of the clinical examination are recorded on the clinical questionnaire II, while the results of the X-ray examination, of the dosimetric determination of thorotrast deposits, and the thorium content of the breathing air as well as the lab data are recorded on the clinical questionnaire III.
3. Recording the data of deceased or lost patients on the final questionnaire. In the case of deceased patients, this information is mostly furnished by authorities or physicians.
4. The results of the re-examinations within the framework of the follow-up study are provisionally recorded on the same questionnaires.

The data in the questionnaires is recorded partly in free text, partly in a coded form. Information that is fixed in free text only is not included in the evaluation. The codes to be used are printed on the questionnaires wherever possible. As a rule, provision is made for simple yes/no-answers for qualitative information, 0 always indicating "no", 1 indicating "yes" and 9 indicating "missing information". Where more than one answer is possible, simple numerical codes were chosen, if the features are exclusive. Where features are not exclusive, the 1-2-4-code is used. Diagnoses are coded according to the KDS-code of clinical diagnoses by Immich.

With quantitative information, the actual figures are entered. The questions on the questionnaires are phrased in such a manner that they can be used both for thorotrast- and control-patients.

The difficulties in tracing thorotrast patients are increased by the fact that with many persons assumed to be thorotrast patients the name of the contrast medium used is not mentioned in the medical record and one may only conclude from the manner of application that thorotrast has been employed. With part of these patients this assumption is confirmed by the subsequent examination, while with others no evidence of thorotrast can be shown. In addition, there is a further group of patients where thorotrast has been used according to the information in the medical record, but where there is no longer any evidence of such application. In order to be able to differentiate among all these possibilities, the code distinguishes the following three groups:

Group 0 = control group

By this we understand those patients where there is no indication what so ever of thorotrast application either in the medical record or in the course of clinical and biophysical examination.

Group 1 = thorotrast doubtful

By this we understand those patients where thorotrast application is suspected, but where there is no longer any evidence of thorotrast today.

Group 2 = thorotrast positive

By this we understand those patients where there is sure evidence of thorotrast today.

Allocation to one of these three groups is, therefore, effected according to the thorotrast findings in the clinical examination. Group 1 forms an inhomogeneous group which, however, has to be taken into consideration in the evaluation. The

case history details furnished by the patient as to whether he knows that he received a thorotrast injection or whether he is of the opinion that he received such an injection are of merely informative character.

The following numbers provide data identification and record linkage:

1. A document-number which is used continuously throughout all medical record questionnaires;
2. a specific identification number referring to the patient which is centrally allocated;
3. a current number of the series of clinical examinations which is allocated by the respective examiner.

The choice of items to be covered in the study gave occasion to numerous discussions and deliberations, in which clinicians, biophysists and statisticians took part. To begin with, first experiences were gained from some hundred thorotrast and control patients within the framework of a pilot study. The final questionnaires were then received with the aid of the results of the pilot study. The most important points of view in the selection of features were the assumed relevancy of information to the problem to be studied, the question of reliability and validity of the information as well as the question of the costs of getting the actual facts.

The following groups of data are mainly covered:

Patient's case history with respect to thorotrast injection and possible surgery or other therapy which might be connected with the thorotrast injection; clinical symptoms which might in any way be related to liver damage, granulomas or loss of nervous functions due to paravascular deposits, thorax X-rays of the empty abdomen and of the contrast medium deposit with localization, dosimetric measurements of thallium-208 in the whole body, liver and spleen and of radon-220 in the air exhaled, haemogram, bilirubin, ferments and bromsulphthalein test. Mean-

while further measurements, such as liver scintigraphy, alpha-fetoprotein and ultrasound diagnostics have been included in the routine.

The decision as to the form in which these new methods as well as the results of the follow-up study are to be incorporated in the statistical evaluation will depend on further tests.

<u>1. Inquiries:</u>	<u>Collected on</u>	<u>Code-N^o</u>
Extract from medical record	medical record questionn- aire	01
<u>2. Patient examination:</u>		
Case history	clinical questionnaire I	02
Clinical examination	clinical questionnaire II	03
X-ray)		
Dosimetry)	clinical questionnaire III	04
Laboratorium)		
<u>3. Termination:</u>		
Data of deceased or lost patients	final questionnaire	05
<u>4. Follow-up:</u>		
Re-examination	provisionally on the same clinical resp. final questionnaires	

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EURATOM.

Actual Status of the German Thorotrast Study

by

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Abstract

The German thorotrast study is a supra-regional "compound-research program", containing clinical and biophysical examinations of thorotrast patients and a control group. The causes of death were ascertained for those thorotrast patients who died later than 3 years after the injection of thorotrast or 3 years after their hospitalization. A follow-up-study was started 1972. Up to now, 12 000 patients belonging to the thorotrast and control group were researched; 800 thorotrast patients and 600 members of the control group were examined. The causes of death were ascertained for approximately 950 thorotrast carriers and 800 persons of the control group. At the present time it appears that thorotrast carriers have a higher incidence of liver tumours, liver cirrhosis, leukemias and aplastic anaemias.

The German thorotrast study is new in relation to the other thorotrast investigations in other countries. Since 1968 we are working in a supra-regional compound research program, in which the following institutions are involved:

- 1) Institute for Nuclear Medicine, German Cancer Research Center, Heidelberg
- 2) Institute of Documentation, Information and Statistics, German Cancer Research Center, Heidelberg
- 3) Institut for Biophysics of the University of the Saar Territory, Homburg
- 4) Nuclearmedical Department of the Clinicum Steglitz of the Free University at Berlin

The thorotrast program is supported by grants from the German Ministry for Science and Technology, and EURATOM.

The German thorotrast study is seriously handicapped as a result of World War II. The records in many hospitals and registration offices were destroyed. Many patients moved repeatedly during, and after the war. Lastly, the division of the country makes it impossible to reach a large number of thorotrast carriers, or obtain their medical documents.

We searched for thorotrast patients in 80 hospitals throughout the Federal Republic of Germany. Our search for thorotrast carriers was, however, only successful in 30 hospitals. Primarily we looked for patients who had received thorotrast for angiography. We also examined 14 patients with thorotrast residues at the site of injection, after fistulography. We found only 2 patients with residues of thorotrast in the region of renal pelvis, after retrograde pyelography. The patients in our study received thorotrast during the years from 1934 to 1949. The control group was selected in each hospital in accordance with the criteria explained by Professor IMMICH.

First of all, I would like to present a short statistical review.

<u>Tab. 1</u>	<u>German Thorotrast Study</u>	
	<u>Thorotrast group</u>	<u>Control group</u>
patients ascertained	6000	6000
patients examined	800	600
patients deceased		
(>3 years post inj.)	950	800
(<3 years post inj.		
resp. not traceable)	4250	4600

To date 6000 thorotrast cases and 6000 control persons were researched. Approximately 80% of these persons have died in the meantime. During the last 4 years we were able to

examine 800 living thorotrast patients and 600 persons of the control group. The cause of death was elucidated for those patients who died more than 3 years after the injection of thorotrast, in the case of control groups more than 3 years after hospitalization. Up to now 950 cases in the thorotrast group resp. 800 cases in the control group, could be traced up to the time of their death. The remaining 4250 persons in the thorotrast group resp. 4600 in the control group, have been disregarded because they died within less than 3 years after the thorotrast injection, or their hospitalization. The most common cause of death in these cases was the disease present at that time. A small number of persons have not been traced up to now, and are still being searched.

The study is not yet finished. The numbers are not permanent, and are still changing. We have consciously evened up the values in order to clearly show the differences in size.

After patients have been found, often after time-consuming correspondence, we sent them a letter inviting them to Heidelberg or Homburg for an ambulant examination. Most patients accepted our invitation, after some hesitation. The control group offered greater difficulties.

The examination includes: anamnesis, general state of health, laboratory findings, X-ray examination of the abdomen, thorax and site of injection. The thorotrast patients as well as the control persons have to undergo whole body counting and determination of the exhaled thoron.

A certain number of patients was not able to come to Heidelberg or Homburg for reasons of old age or illness. These patients are examined in their home by a physician and a biophysist. An equipment in order to measure the exhaled thoron is carried along by car. Excepting whole body counting and X-ray examination all programmed examinations can be performed.

All above mentioned findings are recorded on data sheets. The final evaluation will be done by means of a computer. On this topic Dr. SCHMIDLIN has already reported. The method of examination is identical for both, thorotrast and control patients. Supplementary examinations had been performed or arranged in the sense of small project studies or for clinical reasons. You will understand that no definite statements on the clinical investigations can be given at the present time in order to prevent any influence on the final evaluation by the computer. Some special clinical findings however can be reported subsequently.

The cause of death could be ascertained in 950 patients of the thorotrast group resp. in 800 of the control group who died later than 3 years after injection of thorotrast resp. 3 years after hospitalization.

Tab. 2 Causes of death among deceased patients

	Thorotrast patients (950)	Control patients (800)
liver tumours	78	5
liver cirrhosis	64	22
leukemia	15	2
aplastic anaemia	10	0
tumours of the lung	28	22
tumours of the bone	3	0

Tab. 3 Fatal blood dyscrasias among deceased patients

	Thorotrast patients (950)	Control patients (800)
acute leukemias	13	1
aplastic anaemias	10	0
C M L	2	0
C L	0	1

Information on causes of death we obtained from health offices, from medical death certificates, from hospital records, records of post mortem examination and private notes

of physicians. The figures of the tables demonstrate that primary tumours of the liver, liver cirrhosis and diseases of the bone marrow occur at a much higher frequency in thorotrast patients. Tumours of the liver are to one third hemangioendotheliomas, to one third cholangiocellular- and to one third hepatocellular-carcinomas. The average latent period in the cases investigated by us is about 23 years. Concerning diseases of the bone marrow the incidence of acute leukemias and aplastic anaemias is dominating in the thorotrast group. One case of chronic lymphatic leukemia was, up to now, detected only in the control group. The average latent period of leukemias in this study is only 18 years.

Though thorotrast is highly accumulated in the spleen we did not find, up to now, a single primary tumour of this organ in our thorotrast patients. Lymphosarcomas occur nearly similarly in both groups. The lungs, too, are considerably exposed to radiation. The rate of tumours of the bronchus, however, is not essentially higher than in the control group.

Finally I would mention our follow-up-study which was started some months ago. We re-invited the patients of both groups, who had been examined more than 2 years ago. Approximately 10% of these patients died in the meantime. The cause of death of 30 persons in the thorotrast group resp. 27 in the control group could be elucidated. In the thorotrast group 6 persons died of a primary tumour of the liver and 2 of leukemia. These numbers indicate that the incidence of thorotrast-induced neoplasias is still increasing. It is therefore highly desirable to continue the follow-up of previously studied thorotrast patients in the different countries. We have started our follow-up-study at the end of the last year. Final data sheets are not yet prepared - not without a good reason. It is hoped that the discussion at this international conference might lead to some recommendations for uniformity in data collection in follow-up-studies in all national thorotrast programs. Such an uniformity will permit to compile the data and to perform a world-

wide evaluation of the largest involuntary experiment on radiation effects on humans which ever occurred.

Special Clinical Findings among Thorotrast Patients

by

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Abstract

The outstanding, probably thorotrast-induced, diseases among the 800 examined patients are 4 tumours of the liver, many liver cirrhosis, one case of chronic myeloid leukemia and a lot of long term sequelae caused by paravascular injection. Since the liver is the most commonly injured organ of thorotrast carriers we developed a step-wise diagnostic schedule consisting of laboratory tests, X-ray examinations, sonography, celiac arteriography and laparoscopy. For the necessary follow-up-studies we hope, in this way, to keep the diagnostic stress within tolerable limits, while obtaining satisfying diagnostic results.

Having up to now presented our thorotrast program⁺⁾ from a statistical point of view, let me now report some clinical findings.

We found 4 cases of liver tumours, and one case of a chronic myeloid leukemia 27 years after injection of thorotrast (1). A correlation between these diseases and thorotrast can be considered.

We had one 65 years old patient with an extended hemorrhagic pleural effusion. An extensive paravascular depot in the neck had run far off into the mediastine and even embraced the aortic arch. The suspicion of a thorotrast-induced neoplasia was a reasonable assumption. The careful examination

⁺⁾ Supported by grants from the German Ministry of Science and Technology and EURATOM.

including digital rectal palpation showed a metastasing carcinoma of the prostate with osteoplastic metastasis; a connection with the thorotrastosis surely did not exist.

As to non-neoplastic thorotrast effected diseases we already mentioned numerous forms of hepatopathy ranging from fibrosis to cirrhosis of the liver. We frequently observed long term sequelae caused by paravascular thorotrast deposits. With a latent period from 15 to 25 years these patients had a paresis of the embraced nerves caused by thorotrast granuloma: paresis of the nervus recurrens with hoarsenes; paresis of the nervus sympathicus with classical HORNER-syndrom, sometimes accompanied by paresis of the nervus hypoglossus with atrophy of the related half of the tongue. Deposits which extended far cranially into the neck caused paresis of the nervus accessorius with atrophy of the muscular system of the shoulder. Deposits extending more caudally caused paresis of the phrenic nerve, resulting in a one sided phrenoplegia (2).

The vessels, too, are compressed by the thorotrast granuloma, as for example the vena jugularis. In some cases a suspected occlusion of the carotis was excluded by arteriography; there was a free passage of the contrast medium, and we supposed that the symptoms were caused by another cerebral disease.

A suprainguinal spreading of the thorotrast along the iliacal vessels resulted in a paravascular thorotrast granuloma, which was able to embrace the crossing ureter. The obstruction of the ureters caused stenosis, after a latent period of 15 to 25 years, which resulted in 4 cases to hydronephrosis which necessitated unilateral nephrectomy. In 3 cases the stenosis of the ureter was attended by occlusion of the vena iliaca. The artery seemed to be more resistant to the compressing thorotrastoma (3). In some cases we saw a chronic fistular inflammation around the thorotrast granuloma. We never found sarcoma at the edge of the thorotrast granuloma.

Since the liver is the most frequently injured organ in thorotrast patients we tried to combine various diagnostic methods to obtain a detailed diagnosis; some of these special methods do not belong to our official program.

First our examination program was enlarged to include the determination of alpha-1-fetoprotein, indicating hepatocellular carcinomas (4). We performed this investigation in 200 thorotrast cases and found 2 positive reactions. One of these patients had a hepatocellular carcinoma, the other a chronic myeloid leukemia.

X-ray examination of the upper abdomen is routinely performed on each patient. The evaluation of 500 roentgenograms showed 6 different types of thorotrastosis, which are schematically represented here.

Type 1: Deposits of thorotrast are only visible in the periportal lymph nodes, while liver and spleen give a normal organ shadow.

Type 2: Granular deposits are recognizable in the spleen.

Type 3: Small deposits of thorotrast lie on the edge of the liver. The spleen appears more compact and the number of thorotrast-filled periportal lymph nodes increases.

Type 4: A diffuse, granular or striped pattern of the liver is visible.

Type 5: A coarse-meshed contrast pattern now appears. The liver is exactly visible and the spleen becomes metallic compact with a chain of parasplenic lymph nodes.

Type 6: This group is characterized by massive aggregations of thorotrast particles, sometimes in spider-form figures. The deposits in the liver are irregular and distorted.

It looks as if "type 6" includes changes in the structure of the liver parenchyma in the sense of a liver cirrhosis, often attended by enlargement of the spleen.

One of the patients, examined in 1968 and re-examined in 1972, showed a change from type 5 to 6. Four years ago the

roentgenogram showed a regular meshed contrast in the liver. Now we see thorotrast accumulations and a considerable diminution in the size of the liver with an average reduction of 5 cm in height, accompanied by a simultaneous enlargement of the spleen.

We have compared these types of deposits with the known injected quantities of thorotrast. Type 1 appeared most commonly in cases of paravascular injections, or when the recipients were children. Type 2 was found most frequently among patients who had received 1 or 2 ampules of thorotrast for carotid angiography. Patients classified as type 5 or 6 generally received 40 to 60 ml thorotrast. In our follow-up-study 6 patients died having primary liver tumours. 5 patients belonged to type 5 or 6, only one belonged to type 3.

It must be noted that various methods of X-ray examination will bring somewhat different roentgenograms. Besides, a relation appears to exist between the various types and the quantity of thorotrast deposited in the liver.

Sonographic examinations can only be performed in our institute for a short time. Since this method does not expose the patient to radiation, it is especially appropriated for the examination of thorotrast patients (5). The normal, clinically "sound" thorotrast liver gives no striking sonogram. In cases of irregular tomographic findings a scintigraphy of the liver was performed. Our experience shows that the fibrotic state of the liver cannot be determined by means of sonography, but we had a good correspondence to scintigrams in many cases of liver deforming processes.

The scintigram of thorotrast carriers may be completely normal in spite of large deposits of thorium dioxide; a diffuse fibrosis of the organ, however, cannot be excluded. Only a small number of patients demonstrated scintigraphic changes indicating a liver cirrhosis (6).

A more exact diagnosis in cases of diffuse degenerative alterations in the liver is given by laparoscopy combined

with biopsy under sight, and histological examination of the obtained material. We do not perform blind puncture because of the high risk of intra-abdominal bleeding, since many cases of hemangioendotheliomas have been described in the liver of thorotrast carriers. Moreover, the blind puncture often fails to reveal a liver cirrhosis (7).

The celiac arteriography is especially appropriate to recognize neoplastic diseases in the liver because most of thorotrast-induced liver tumours are highly vascularised. This method has an advantage over the laparoscopy, in that the whole organ can be seen. Some of our patients showed circumscribed accumulation defects in the scintigram in the region of a big thorotrast deposit. We then performed celiac arteriographies, without finding a tumour. We suspect that scarring and hyalinisation occurs at the site of the thorotrast deposit, and that this tissue is similar to a thorotrast granuloma. The only operable tumour of the liver discovered by celiac arteriography was a cholangiocellular carcinoma (8;9).

The thorotrast population has a high risk in developing degenerative and neoplastic diseases of the liver. The necessary control examinations should not be a stress for the patient. The examination carried out in different steps, beginning with an exact physical and laboratory examination, keeps the patients' stress in tolerable limits, while giving satisfying diagnostic results.

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Medical Problems Concerning the Control Group

by

D. Lorenz, W.J. Lorenz and G. van Kaick

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German Cancer Research Center Heidelberg**Abstract**

Within the German Research Project THOROTRAST besides patients who have received a Thorotrast injection there were also examined patients of a control group, which was selected according statistical points of view. It is reported about the difficulties and problems which occur at the performance of the examination of the control group.

Introduction

The control group in the German Research Project THOROTRAST is composed of patients whose names begin with the letter B, and who were treated at the same time and in the same clinic with the patients having received Thorotrast. Professor Imrich and Dr. Schmidlin have reported in detail about the selection of these patients. The patients of the control group are examined in an identical way to the Thorotrast patients.

Performance of the Study

Difficulties with the control group of the research endeavor begin with the gathering of clinical data within the clinics. Clinic directors reluctantly gave insight into the documents of the Thorotrast patients, understanding the necessity, but often made it difficult to obtain informations on patients of the control group. Most clinic directors are not convinced of the necessity to examine patients in the control group, and are afraid that this might violate the physician's code of ethics. The first, and often the most difficult problem facing our co-workers, who make the patient investigations, consists in overcoming this resistance, and in convincing the directors of the necessity for the control group.

The problems associated with the second phase result, when patients who were selected, according to statistical conditions, are found again, and were sent a first letter. This letter informs the patient that our investigations had discovered that he had been in a particular clinic at a specific time, and that we are interested in his present state of health, and in his health during the intervening period of time. Simultaneously we ask the patient to fill out a questionnaire.

Most patients answer the questions willingly. Some patients, however, are disturbed by our investigation and ask for clarification. In this group are especially those patients who were previously treated in neurologic or psychiatric clinics. Their clinical treatment is an unpleasant memory to these patients, especially if they have married in the meantime.

In a second letter we give the patient the information asked. Simultaneously we explain the reason for the investigation. We inform the patient that we would like to invite him to a free, precautional, examination. Many patients quickly decide to come to Heidelberg (HD). Others, however, are sceptical and seek the advice of their relatives, or their family physician. Most physicians recommend that the patients take advantage of the check-up. In some cases it is only the intervention of the family physician which persuades the patient to travel to HD. However,

some family physicians dissuade the patients with the argument that they are only to be used as guinea-pigs. Fortunately only very few patients permitted themselves to be negatively influenced, and come to the check-up. Some even come against the advice of the family physician. The fear to be a guinea-pig is, however, subconsciously present in almost all patients. This is the reason for explaining to the patients, in our letter of invitation, the exact procedure of the examination.

The examination consists of three parts, a clinical, a radiological, and a biophysical examination. With the exception of a single blood withdrawal from the vein of an arm, our patients are not inconvenienced. Most patients are alert to any changes in the examination, and expect the examination to progress in the promised manner. This is especially true if a lumbar puncture, a suboccipital puncture, or an encephalography has previously been performed. The willingness of patients to subject themselves to this examination is also correlated to age, sex, social status, present state of health, and the desire to travel. Elderly people in retirement, who are active and healthy generally enjoy coming to HD for their check-up. Self employed persons are generally not easily persuaded to come.

Once a patient has made the decision to come for the check-up, it is important that he is welcomed, and is accompanied by one of our co-workers for the various examinations.

The clinical examination offers the most important contact between patient and physician. The physician attempts to win the confidence of the patient, and to overcome the last resistance against the check-up. This is best accomplished while the case history is obtained. Then follows a physical examination, for which we reserve sufficient time. This method tends to bring about, in nearly all cases, a favourable patient-physician-relationship. This is expressed by favourable remarks of the patients, and their letters of thanks. When we began with our follow-up examinations last year we received unusually large numbers of acceptances, to the examination. The patients who came for their second examination to HD regularly asked to be reconsidered for a third check-up.

The family physician of the patient receives a detailed letter with the results of the examination. This letter contains the most important anamnestic dates and results of the check-up. We also make suggestions for further diagnostic steps, and give recommendations for the treatment of the patient.

From the physician's point of view, however, the follow-up examination, of the patients in the control group, is unsatisfactory for the following reasons:

Due to the Thorotrast Research Project's examination scheme the patient is only in HD for a few hours of one day. For this reason the out-patient diagnostic work must remain incomplete in many cases. Should we, for example, discover a hypertonic disease, we are not able to perform all the necessary examinations to find out the reason for this disease. Therefore we must request the family physician to take care of the final diagnostic work. It is also impossible for us to perform the treatment. We can only give some therapeutical recommendations to the family physician. The work with the family physician is, in most cases successful, especially after the completed examination. Thus the diagnostic and therapeutic recommendations are generally accepted. After we have examined their patients, the physicians do not longer look upon us as competitors. Moreover we have the impression that the family physicians consider us to be an unexpected but acceptable assistance.

A further problem of the control group is the fact that many persons having come to HD were made to "patients" by us. These patients felt healthy and did not have the intention to go to a physician. The subjects discovered during or after our examination made a treatment for an illness necessary.

Results

We now have the first results of the examination of the control group. Preliminary, and very careful, evaluations show that coronary and vascular diseases are most common. The second po-

sition is taken by diseases of the liver. The pulmonary organs, gastrointestinal discomfort, excessive weight, diabetes, degenerative diseases of skeleton, gall bladder diseases, and disfunction of the kidney and the urogenital system follow. One of our patients had a circumscribed ovarian carcinoma, which was still operable. Bone marrow diseases and acute leukaemia were not found in patients of the control group. Two patients of the control group had a thorotrastosis. In arriving at this diagnosis it was shown how important it is that all patients of the control group are examined with the whole body counter.

Case Reports

Our report shall end with three case reports. These cases are examples for the fact, that some patients of the control group suffered from serious diseases which were unknown to them. In June 1970 we examined a 70 year old woman and found a tumour in the left lower abdomen, and an enlargement of the corresponding inguinal lymph nodes. We therefore requested that the family doctor refer the patient immediately to a gynaecologist. One month later this patient was operated on a left sided circumscribed malignant, ovarian tumour. A postoperative therapy was carried out with Endoxan. At the present time the patient's condition is good.

The follow-up examination of a 55 year old man resulted, in a diagnosis of tachyarrhythmia absoluta with atrial fibrillation, ventricular extrasystolia, severe left sided myocardial damage, severe hypertonia, symptoms of coronary decompensation in the sense of lung and liver congestion, suspected enccephalopathia due to high blood pressure and peripheral vascular obstruction. Because of his poor state of health we immediately referred the patient - supported by the family physician - to a hospital.

One 80 year old man was found to have a Morbus Paget. We made the diagnosis during the follow-up examination. The radiological examination revealed the typical changes in the area of the pelvic bones, with a distinct kyphoscoliosis of the thora-

cical vertebral column and with a greatly increased alkaline phosphatase.

Conclusion

Summarizing, we are able, to say that the follow-up examination of patients in the control group of the Thorotrast Research Program is extremely advantageous also from the physician's point of view since many cases of undiagnosed diseases were discovered which led to therapeutic measures. In this manner an originally conceived method for statistical purposes resulted in work of great value for the individual patient.

Acknowledgements

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THOROTRAST INJURY IN JAPAN

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Thorotrast injuries in Japan occurred after 1945, of which 94 autopsy cases were accumulated up to 1970. These autopsy cases consisted of 60 cases of malignant tumor of the liver and 9 cases of blood diseases. Examination of Thorotrast-administered autopsy cases in Japan has revealed, among other things, that about one half of all Thorotrast-administered cases were war-wounded ex-servicemen and that the dates of injection in these were concentrated between 1932 and 1944. Based on this preliminary finding, the authors conducted a follow-up study on 147 Thorotrast-administered war-wounded ex-servicemen after a lapse of 31 to 36 years from Thorotrast injection, and found that 6 cases of malignant tumor of the liver, 1 case of leukemia, 1 case of thrombocytopenic purpura and 5 cases of cirrhosis of the liver had occurred among the samples. The incidence of these diseases in the samples was shown to be significantly higher than that in the controls. Further, clinical examination was conducted on 45 samples selected from among the above mentioned 147 Thorotrast-injected war-wounded ex-servicemen. In liver function test, lowering of protein metabolic rate and foreign body discharge function was observed, while blood examination indicated decrease of erythrocytes, leucocytes, hemoglobin value and thrombocyte count. These findings in the samples were significant in comparison with the controls. Finally, the total number of Thorotrast-administered persons living in Japan as of 1972 was roughly estimated at 5,000.

Introduction.

Thorotrast has been used clinically in Japan between 1928 - 1954.

After 1937 this contrast medium was used chiefly in former army hospitals for the diagnosis of traumatic diseases in war-wounded servicemen.

In 1945, the first report of Thorotrast injury was hepatic cirrhosis, discovered after autopsy (11). In 1951, the first occurrence of hepatic cholangiocarcinoma following Thorotrast administration was reported (12). Since then, a number of reports on Thorotrast injuries have been collected.

In studying Thorotrast injury cases in Japan (3, 7) the authors conducted a survey of available autopsy records of persons known to have been given Thorotrast. About half of these were war-wounded ex-servicemen injected with Thorotrast for diagnostic purposes at former army hospitals.

A follow-up study of some of these war-wounded ex-servicemen was undertaken.

1. Survey of Thorotrast-administered Autopsy Cases in Japan.

Between 1945 and 1970, a total of 94 Thorotrast-administered autopsy cases were collected, consisting of 77 males and 17 females.

The ages of these autopsy cases at the time of Thorotrast administration ranged from 5 to 59 years. The ages of all Thorotrast-administered cases at the time of death ranged from 35 to 72 years.

Of the 87 Thorotrast-administered autopsy cases reported between 1958 and 1970, 73 are recorded in the Annals of Pathologi-

cal Autopsy Cases in Japan^{*)}.

From these records the ratio of Thorotrast-administered autopsy cases to the total autopsy cases by causes of death was as follows: Malignant hepatic tumor - 0.5%; Leukemia - 0.1%; aplastic anemia - 0.4%; hepatic cirrhosis - 0.1%; lung carcinoma, pancreatic carcinoma, bone sarcoma and malignant retroperitoneal tumor - 0.1 - 1.4%.

Kitabatake (6) has observed Thorotrast deposition shadows in 0.9% of all living cases of malignant hepatic tumor whose X-ray films he has examined. This figure is in close accordance with the results obtained in this study of autopsy cases.

A breakdown of Thorotrast-administered cases by causes of death is given in Table 2. Of the 94 cases listed in this table, Thorotrast administration is considered a factor in the causes of death in 91 cases.

Among the various malignancies, Thorotrast-induced malignant hepatic tumors are, as shown in Table 3, exhibit a histological incidence markedly different from that of non-Thorotrast-induced primary malignant hepatic tumors. (7). For example, the ratio of incidence between Thorotrast-induced and non-Thorotrast-induced cholangiocarcinoma is about 10:1, while that of liver cell carcinoma is 1:11. Also, hemangioendothelioma of the liver, which ordinarily accounts for only 0.2%, that is, one out of 500 malignant hepatic tumors, occur in 10 of the 60 Thorotrast-administered cases.

*) The Annals of Pathological Autopsy Cases in Japan have been annually compiled and published by the Japanese Pathological Society since 1958. The latest issue thus far published in the 1970 edition.

nistered autopsy cases.

The time intervals between Thorotrast administration and the onset of malignant hepatic tumors were 11 to 35 years in the 34 cases for which this information was available. The average latent period between the group given large amounts (40-100 ml) of Thorotrast did not differ from the group given small amounts (5-39 ml).

As to the 9 autopsy cases of blood diseases, these consisted of three cases of acute or subacute myeloid leukemia, two cases of erythroleukemia and four cases of aplastic anemia. It is highly interesting to note that erythroleukemia, a very rare blood disease in Japan, was discovered in two out of the nine cases (Table 2). In those of the cases on which chromosome examination (12) was conducted, an increase of abnormal chromosomes was observed.

Thorotrast-induced fibrosis of the liver, spleen and upper abdomen lymph nodes was observed in almost all cases, frequently resulting in the reduction of the liver weight to less than 800 grams and in "chalk Spleen" weighing less than 20 grams. Fibrosis of the liver, (Thorotrast cirrhosis), was the proximate cause of death in 12 cases, accounting for 12.8% of the causes of death in the total Thorotrast-administered autopsy cases.

To summarize, the foregoing results of our survey of Thorotrast-administered autopsy cases in Japan has disclosed a high incidence of malignant hepatic tumors, cholangiocarcinoma and hemangioendothelioma in particular, along with frequent occurrence of blood diseases, and the presence of liver and spleen fibrosis in nearly all of the cases.

2. Follow-up Study on 147 War-wounded Ex-Servicemen Given Thorotrast.

A. Follow-up Study:

From a survey of 15,000 case history records, mostly pertained to war-wounded ex-servicemen, a total of 147 cases of Thorotrast administration were collected.

From 1963 to 1964, that is, 22 to 27 years after Thorotrast was administered to the 147 cases a follow-up study was conducted. By means of a questionnaire 139 of these cases were traced, of whom 112 were alive.

Then, from 1972 to 1973, that is, 31 to 36 years after Thorotrast administration, the authors conducted a second follow-up study, this time obtaining information about 142 cases of which 85 were living.

Of these 133 had been given Thorotrast intravascularly and these formed the study groups.

The Thorotrast-administered group had been given Thorotrast between 1937 and 1943. (Fig.4). Their ages at the time of administration ranged from 20 to 39 years, but 83% had received injection at ages between 20 and 29.

The diseases which had originally led to the injection of Thorotrast were traumatic diseases in 131 cases. The majority of these were traumata of the head and cervical region and traumatic aneurysm in the upper or lower extremities. The amount of Thorotrast administered per patient ranged from a minimum of 5 ml to a maximum of 75 ml. (Fig.6).

By causes of death, malignant tumors in the Thorotrast-administered group accounted for 11 cases including 6 malignant hepatic tumors, 3 cases of gastric carcinoma, 1 case of rectal car-

cinoma and 1 case of laryngeal carcinoma, while blood diseases accounted for 2 cases (one case each of acute myeloid leukemia and thrombocytopenic purpura), liver cirrhosis for 6 cases and other diseases for 22 cases. Causes of death could not be known or determined in the remaining 11 cases.

As causes of death, malignant hepatic tumors in the second follow-up study included 3 cases of cholangiocarcinoma, 1 case of hemangioendothelioma and 2 cases of liver carcinoma, against 3 cases of cholangiocarcinoma in the first follow-up study. Non-hepatic malignant tumors as causes of death, not found in the first follow-up study, included 3 cases of gastric carcinoma, 1 case each of rectal carcinoma and laryngeal carcinoma in the second follow-up study. The number of fatal blood diseases - one case each of myeloid leukemia and thrombocytopenic purpura remained unchanged between the first and the second follow-up study, while liver cirrhosis increased from 2 cases in the first follow-up study to 5 cases in the second. Deaths due to other diseases also increased from 13 in the first follow-up study to 22 in the second. (Table 7).

Control groups and control population:

War-wounded ex-servicemen who had been inmates in the same hospitals at about the same time as the Thorotrast-administered cases but who had been given sugiuron (an organic iodine contrast medium) were compared with the Thorotrast-administered group, (control Group A). Likewise, 1,330 ex-servicemen who had never been given any contrast medium were selected as Control Group B. Further, based on the Welfare Ministry population statistics (14), Japanese males in the same age bracket as the Thorotrast-administered cases, that is, males aged 20 to 44 years in 1940, were selec-

ted as a Control Population.

Control Group A was used to study the effects of war injuries plus non-radioactive contrast medium, and Control B to study the effects of war injuries per se. The Control Population, meanwhile, was made to serve as basic controls against the Thorotrast-administered group and Control Groups A and B.

Compared with Control Group B and with the Control Population, the Thorotrast-administered group exhibited a significantly higher mortality rate.

As for mortality rate for diseases, the Thorotrast-administered group contained a significantly larger number of deaths due to malignant hepatic tumor than the Control Group B and the Control Population at a critical level of 0.5% and significantly larger number of deaths due to leukemia and liver cirrhosis than Control Population at a critical level of 5%. No significant difference was found to exist among the controls except liver cirrhosis between Control Group B and Control Population. (Table 10).

Mortality rate of blood diseases was significantly increased in the Thorotrast-administered Group than in the Control Group B and Control Population (a critical level of 5% in the former and 0.5% in the latter).

B. Clinical Examination Cases Given Thorotrast:

45 cases who had been injected with Thorotrast were selected from among the cases under follow-up study and clinically examined in comparison with 32 controls selected from the same sample frame. These two clinically examined groups are hereafter referred to as "clinical" Thorotrast-administered group and "clinical" control group, respectively.

1. X-ray examination of upper abdominal region:

X-ray films of the upper abdominal region were taken of 44 of the 45 "clinical" Thorotrast-administered cases, revealing lymph node shadows in 43 cases. Among these, shadow of the spleen was observed in 36 cases and Thorotrast deposition shadow of the liver in 28 cases. The single case in which Thorotrast deposition shadow was not observed in any of these organs or lymph nodes was a case who had been administered 5 ml of Thorotrast. No abnormal X-ray film shadow was observed in any of the "clinical" controls. (Table 14).

2. X-ray films of Thorotrast injection sites:

X-ray films of Thorotrast injection sites were taken of 40 of the 45 "clinical" Thorotrast-administered cases, revealing residual shadows in 18 cases. Palpation also revealed the presence of Thorotrastoma at injection sites in these cases. (Table 14).

Of these, 7 had Thorotrastoma in the cervical region, 7 in the upper extremities and 4 in the lower extremities. In two of the cervical Thorotrastoma cases vocal cord paralysis and paralysis of nerve recurrens were also present, while two of the upper extremity Thorotrastoma cases were accompanied by impairment of motor capacity.

3. Radioactivity measurement by use of scintillation counter:

Linear scanning was conducted by use of a scintillation counter on 20 of the "clinical" Thorotrast-administered cases, revealing the presence of radioactive substance in 8.

The scanning values showed a marked rise in the upper abdomen and at Thorotrast injection/extravasation sites. However,

cases, who had been given large amounts of Thorotrast did not necessarily prove positive in scanning, which made it difficult to ascertain the existence of any definite relationship between the amounts administered and the scanned radioactivity levels. (Table 14).

4. Liver function test:

Liver function test was conducted on 40 "clinical" Thorotrast-administered cases and 31 "clinical" controls, revealing disorders of protein metabolism and foreign body discharge function in the former. As regards protein metabolism, while no significant difference was noted between the "clinical" Thorotrast-administered group and the "clinical" control group in the amounts of total serum protein and albumin or in the zinc sulfate test and thymol turbidity test results, decrease of A/G ratio to less than 1.29 was seen in 19 out of 36 "clinical" Thorotrast-administered cases and in 4 out of 31 "clinical" controls.

As for the serum globulin test, increase in excess of 3.48 g/dl was observed in 15 of 36 "clinical" Thorotrast-administered cases as against 4 out of 31 "clinical" controls. In protein fraction, studied for 13 "clinical" Thorotrast-administered cases, showed decrease of albumin in 10, increase of alpha-globulin in 12 and increase of gamma-globulin in 7. To sum up, protein metabolism in Thorotrast-administered cases was characterized by a lowering of A/G ratio and an increase of serum globulins, particularly alpha- and gamma-globulins.

In the foreign body discharge function test, examination of bromsulfalein (BSF) 45 min. value showed an increase of over 6% in 14 of 33 "clinical" Thorotrast-administered cases, but no such

increase was observed in any of the 5 "clinical" controls examined. The rate of increase in the "clinical" Thorotrast administered group was low (up to 14%) in 11 cases and high (15%-30%) in 3 cases.

Enzyme activity was examined with respect to GOT, GPT, alkali-phosphatase and amylase, bile metabolism with respect to urine urobilinogen, and serum lipid with respect to serum cholesterol. These tests revealed no significant difference of results between the "clinical" Thorotrast-administered group and the "clinical" control group. (Fig. 8).

5. Peripheral blood examination:

Peripheral blood examination was conducted on 38 "clinical" Thorotrast-administered cases and 22 "clinical" controls. With regard to the cases where leukocyte count was found to have decreased to less than 4,000 erythrocyte count to less than 3,500,000, hematocrit to less than 40% and hemoglobin to less than 80%, no significant difference was noted between the control group. However, compared with ordinary Japanese males in the same age bracket, the incidence of anemic, hemoglobinopenic and leukopenic cases was significantly higher in the "clinical" Thorotrast-administered group at a critical level of 0.1% 0.1% 0.1% and 5%, respectively.

In 10 out of 26 "clinical" Thorotrast-administered cases and 1 out of 19 "clinical" controls, thrombocyte count was found to have decreased to less than 100,000 (Fig. 9, Table 17)

6. Urine analysis:

In the general urine test, urobilinogen positive (+ to +++) results were obtained in 7 (25,9%) out of 27 "clinical" Thoro-

trast-administered cases, but no abnormal manifestations were found in any of the "clinical" controls.

In summary, the results of the foregoing clinical examination were as follows:

In the cases who had been intravascularly injected with Thorotrast in amounts in excess of 5 ml per capita, X-ray film of the upper abdominal region revealed Thorotrast deposition shadows in the liver, spleen or upper abdomen lymph nodes at a detection rate of 97.7%. Scanning by scintillation counter, meanwhile, revealed Thorotrast deposition in 40% of the cases.

Thorotrastoma was found to have occurred in 45.0% of the subject cases. Liver function test revealed protein metabolism disorders and a lowering of foreign body discharge function, while a decrease of hematocrit value and thrombocyte count was observed in blood test.

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Fig. 2.

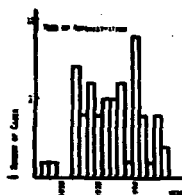


TABLE 1

RATIO OF THIOTRAST-ADMINISTERED AUTOPSY CASES TO TOTAL AUTOPSY CASES RECORDED
IN THE ANNALS OF PATHOLOGICAL AUTOPSY CASES IN JAPAN
(1950 — 1979)

CAUSES OF DEATH	AUTOPSY CASES			LIVER CASES (KITAHARA, 1965)		
	TOTAL NUMBER OF CASES	THIOTRAST- ADMINISTERED CASES	RATIO (%)	TOTAL NUMBER OF CASES	THIOTRAST- ADMINISTERED CASES	RATIO (%)
MALIGNANT TUMORS						
MALIGNANT LIVER TUMOR	2748	46	0.526	466	4	0.86
PANCREAS CARCINOMA	3649	2	0.055	—	—	—
LUNG CARCINOMA	14083	1	0.007	—	—	—
BONE SARCOMA	201	1	0.498	—	—	—
MALIGNANT RETRO- PERITONEAL TUMOR	141	2	1.418	—	—	—
FIBROSARCOMA	364	1	0.275	—	—	—
BLOOD DISEASES						
LEUKEMIA	4682	5	0.107	—	—	—
APLASTIC ANEMIA	929	4	0.431	—	—	—
LIVER CIRRHOSIS	10528	8	0.076	—	—	—
OTHER DISEASES	128459	3	0.002	—	—	—
TOTAL	282790	73	0.026	—	—	—

TABLE 2

Breakdown of Thorotrast-administered Autopsy Cases
by Cause of Death

Cause of Death	Thorotrast-administered Autopsy Cases	
	Number of Cases	Ratio (%)
Malignant Tumors :	70	74.5
Malignant liver tumor	60	63.9
Carcinoma of gall bladder	1	1.06
Carcinoma of pancreas	2	2.1
Carcinoma of lung	2	2.1
Malignant retroperitoneal tumor	2	2.1
Fibrosarcoma at injection site	1	1.06
Triple tumor of liver carcinoma, thyroid carcinoma and gastric tumor	1	1.06
Sarcoma of bone	1	1.06
Blind diseases :		
Leukemia	5	5.26
Acute myeloid leukemia	2	2.1
Subacute myeloid leukemia	1	1.06
Erythroleukemia	2	2.1
Aplastic anemia	1	1.06
Liver Cirrhosis	12	12.8
Others :	7	7.19
Hepatitis	1	1.06
Stomach ulcer	1	1.06
Cerebral hemorrhage	1	1.06
Total	94	100.0

TABLE 3

Comparison of Thorotrast-induced and Non-Thorotrast-induced
Malignant Hepatic Tumors in Autopsy Cases

Histological Classification	Thorotrast-induced		Non-Thorotrast-induced (%)		χ^2 -Value
	Number of Cases	Ratio (%)	Number of Cases	Ratio (%)	
Liver Cell Carcinoma	5	8.1	391	90.9	222.9000
Cholangiocarcinoma	43	71.7	29	7.1	167.9000
Carcinoma of Mixed Type	2	3.3	8	2.0	0.9
Hemangioendothelioma	10	16.7	0	0	67.9000
Total	60	100.0	408	100.0	

*** Confidence of significant level of 0.5%

FIG. 6

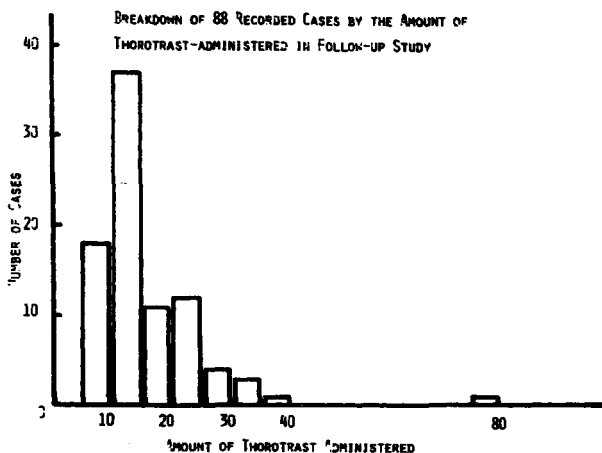


TABLE 7

Comparison of First and Second Follow-up Study
in Relation to Causes of Death

	First Follow-up Study (1963-1964) 133 Cases	Second Follow-up Study (1975-1977) 133 Cases	Increased Number in the Period During 1965-1977
Malignant Tumor	3	11	8
Liver Tumor	3	6	3
Other Tumor	0	5	5
Blood Diseases	2	2	0
Myeloid leukemia	1	1	0
Thrombocytopenic purpura	1	1	0
Liver Cirrhosis	2	5	3
Other Diseases	15	22	9
Accident and War Injuries	1	2	1
Unknown/ Undetermined	6	11	5
Total	27	59	26

TABLE 10

STATISTICAL ANALYSIS OF THE DEATH IN THE
THOROTRAST-ADMINISTERED GROUP AND CONTROLS (Follow-up Study).
— χ^2 VALUE—

CAUSES OF DEATH	THOROTRAST- ADMINISTERED GROUP	THOROTRAST- ADMINISTERED GROUP	THOROTRAST- ADMINISTERED GROUP	CONTROL GROUP A	CONTROL GROUP B
	CONTROL GROUP A	CONTROL GROUP B	CONTROL POPULATION	CONTROL POPULATION	CONTROL POPULATION
MALIGNANT TUMOR	3.3	1.1	3.1F	1.2	1.0
LIVER TUMOR	1.8	15.5 ***	36.92 ***	0.6	0.1
OTHER TUMOR	1.2	0.6	0.17	2.1	1.4
BLOOD DISEASES	1.2	5.0 *	28.46 ***	0	0.2
LEUKEMIA	0.6	1.4	6.2 *	0	0.1
THROMBOCYTO- PENIC PURPURA	0.6	4.7 *			
LIVER CIRRHOSIS	3.2	2.7	16.21 ***		

* CONFIDENCE AT SIGNIFICANT LEVEL OF 5 %

** CONFIDENCE AT SIGNIFICANT LEVEL OF 1 %

*** CONFIDENCE AT SIGNIFICANT LEVEL OF 0.5 %

TABLE 14

CASES FOUND TO HAVE THOROTRAST DEPOSITS IN "CLINICAL"
THOROTRAST-ADMINISTERED GROUP

METHOD	DEPOSITION SITE	CASES EXAMINED	CASES WITH DEPOSITS	
			NUMBER	RATIO (%)
X-RAY	UPPER ABDOMEN			
	LIVER	44	28	63.6
	SPLEEN	44	36	81.8
	LYMPHNODES	44	43	97.7
	INJECTION SITE	40	18	45.0
SCINTIGRAM		20	8	40.0

Fig. 8

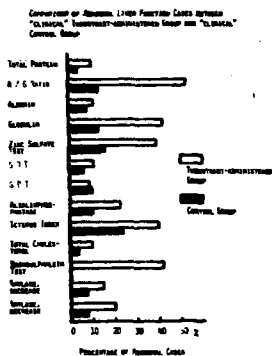


Fig. 9

COMPARISON OF ABNORMAL BLOOD CASES BETWEEN "CLINICAL" THOROTRAST-ADMINISTERED GROUP AND "CLINICAL" CONTROL GROUP

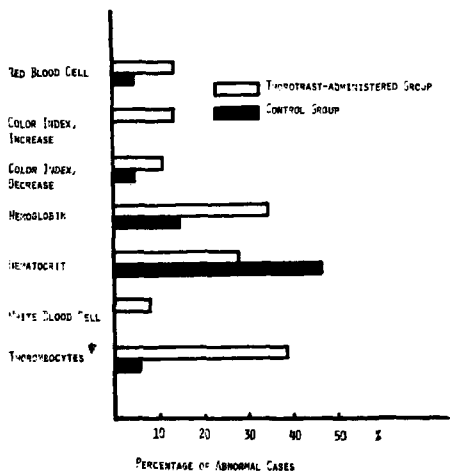


Table 17.

Table Statistical Analysis of Blood Examination of "Clinical" Study
 χ^2 Value

Item	"Clinical" Therofast- administered Group	"Clinical" Control Group	"Clinical" Therofast- administered Group	"Clinical" Control Group	"Clinical" Therofast- administered Group	"Clinical" Control Group
Red Blood Cell	1.14		10.24 ***		0.66	
Hemoglobin	3.01		11.84 ***		2.73	
Hematocrit	1.39					
White Blood Cell	1.82		5.98 *		0.02	
Thrombocyte	0.55 *		11.11 ***		0.82	

* Confidence at significant level of 5 %

** Confidence at significant level of 1 %

*** Confidence at significant level of 0.5 %

Epidemiological Follow-up Studies of the Portuguese Thorotrast
Series (up-dated results).

by

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Abstract.

Epidemiological studies in Portugal of about 51% of 2.500 patients injected with Thorotrast mainly for cerebral angiographies between 1930 and 1955, and of a smaller group of controls (injected for similar purposes with non-radioactive contrast drugs), followed up until the end of 1972. The Thorotrast population has shown a gross excess of malignancies and of severe fibrosis in the liver and in the tissues around blood vessels where the drug intended for intravascular use has been spilled and retained. According to a statistical analysis of the Portuguese data, the excess malignancies are leukemias and other rapidly fatal blood dyscrasias, liver tumours of which the most frequent type is the haemangioendothelioma which is practically "Thorotrast specific" and the total number of malignant tumours, even excluding liver tumours. There is a slight excess of lung cancer too.

The findings are discussed at some length, particularly the significance of local granulomata, liver fibrosis (causing a clinical picture similar to that of liver cirrhosis), fatal blood dyscrasias, liver tumours, lung cancer and malignant bone tumours.

Introduction.

The Portuguese Thorotrast research group comprises within its experience the biggest group of individuals injected with thorium dioxide followed up for the longest period of time recorded. An appreciable number of cases (about half of all the injected) have been lost in the 40 years and more of possible follow-up and the lack or at least modesty of dosimetry studies due to lack of local facilities restrict in part the value of its experience. The total number of cases followed since injection and the statistical and epidemiological data collected have however contributed to the interest and importance of the data collected until now by the "Portuguese Thorium Dioxide Research Group".

Although data from the pathological and epidemiological investigations carried out by the Portuguese Thorotrast Study Group have been published in some papers (1,2,3,4,5,6,7,8,9) and presented at a few international meetings we thought it could have some interest to up-date the results and to summarize the data so far ascertained in the epidemiologic study of the Thorotrast series which began in Portugal in the early 1960's.

In this communication we will only summarize, in a brief form and with the help of a few tables, the statistical results ascertained and up-dated until the 31st December 1972.

Methodology of the epidemiologic study.

The basic data for the approximately 2.500 patients known to have received Thorotrast in Portugal, come from the records of certain Portuguese hospitals (mainly from Lisbon) where that drug had been used as a radiological contrast medium from 1930 to 1955, mainly for cerebral angiographies (Table 1).

Because Thorotrast was much more widely used in hospitals than any other intravascular radiological contrast drug between 1930 and 1950, especially for cerebral angiographies, it was impossible to collect a perfect control group. However, in order to improve the estimate of risk for possible Thorotrast sequelae, a partial control group of patients matched for age, sex and general type of disease at the time of investigation, but injected with a non-radioactive control drug was assembled from patients systemically injected between approximately 1940 and 1955 - although a few have been injected between 1930 and 1940. It was possible in this way to collect 1960 control case records, in the same manner and from the same hospital as the Thorotrast cases (Table 1).

The method of tracing the cases for subsequent investigations which was identical for both Thorotrast and control population has already been described (3,7).

Results.

Until the end of 1972, the results of the epidemiological investigation and follow-up studies of both Thorotrast and control populations can be summarized in the following Tables (Tables 1 to 7).

Success of tracing and follow-up of the cases (Table 1).

Of the 2.433 individuals who have received Thorotrast, 1.231, that is almost 51%, have been traced and are either alive or certified dead. The percentage of successful tracing according to type of injection (Table 1) vary, being highest for the systemically injected cases (1.039 among 1.918 cases, that is 54%) and smallest for the peri-nasal installation cases (192 among 515

cases, that is 37%). Traced cases appear to be distributed approximately in the same manner as the complete Thorotrast group as has been reported previously (4,5).

Tracing was somewhat less successful with the control population, probably because fewer basic data were available. Only 797 cases, that is about 41% of the total number of controls, were traced (Table 1). Also here the traced cases are distributed approximately in the same manner as the complete control population according to the analysis reported elsewhere (5).

Number and causes of death (Tables 2, 3, 4, and 5).

Among the Thorotrast and control cases traced the causes of death and other lesions considered as probably due to late effects of a radioactive internal emitter permanently retained in cells of R.E. System according to our previous knowledge of Thorotrast movement within the human body and its local action, were mainly the following: malignant tumours in liver and other R.E.S. organs, leukaemia and other serious blood dyscrasias, other malignancies, liver fibrosis and local granulomata. These last lesions were found in the tissues where the drug intended for intravascular use was accidentally spilled.

Of the 1.231 Thorotrast cases traced, 918 (74.5%) had died by the end of 1972 (Table 2). 664 of these, that is about 72% of the dead, died of causes apparently not related to the radioactive contrast agent - many of them within the first five years after the Thorotrast installation from the disease for which the drug was used as a diagnost tool (*). In 77 individuals (8.4%)

*) In principle, malignancies occurring within these first five years were discarded and considered "not related".

the cause of death could not be ascertained with a reasonable degree of accuracy. Finally, in 177 (19.3%) the certified and as far as possible (even by autopsy) ascertained cause of death was due to disease or condition considered as very probably related to the specific radioactive effect of the Thorotrast absorbed and retained in the R.E.S. (*). If we consider only the 892 (85.9%) deaths certified among the 1,039 systemically injected cases so far traced, the number and percentage of deaths attributed to totally unrelated causes, unknown causes and causes possibly related to the radioactive effect of Thorotrast were respectively: 644 (72.2%), 74 (8.3%) and 174 (19.5%) (Table 2). Of the 26 deaths registered among locally injected cases, only 3 (11.5%) could be attributed to Thorotrast (Table 2).

Among controls, 545 i.e. (68%) had died by the end of 1972 and the number and percentage of deaths attributed to the same three "groups of causes" - "unrelated", "unknown" and "suspected" - were respectively: 495 (90.8%), 32 (5.9%) and 18 (3.3%). This last percentage should be compared with the corresponding one among Thorotrast cases - almost 18% (Table 2).

The main causes of death ascertained among the 1,231 Thorotrast cases traced, are shown in the first column of Table 3. Only local granulomata, liver fibrosis, leukaemias and other malignancies, especially liver tumours, are specified among the "suspected" causes of death in this table, since these seem like-

(*) Leukaemia and other fatal blood dyscrasias, malignant tumours (especially liver tumours), liver fibrosis and fatal consequences of local induced granulomata.

ly to be associated with the radioactivity of Thorotrast retained in the body for years and could therefore be considered as late effects or long-term sequelae of this drug. In the same table the number of deaths observed among controls is given according to the same causes of death mentioned above (Table 3).

As it can be seen the proportion of deaths attributed to leukaemia and other quickly fatal blood dyscrasias and to malignant tumours among Thorotrast cases is very high indeed. Particularly striking is the number of liver tumours, of which the haemangioendothelioma is the more frequent type found among the cases with histological confirmation (Table 4) and practically "Thorotrast-specific". In fact among 12.835 autopsies and 88.001 biopsies performed by one of the authors at the Faculty of Medicine of Lisbon, during more than 35 years, of the 17 liver haemangioendotheliomas found all but one were diagnosed as Thorotrast cases.

Of the 192 cases who have received the drug locally death was attributed to Thorotrast only in 3 (Table 3). In two cases death was due to a malignant tumour developed on the edge of a Thorotrast induced local granuloma: a carcinoma of the rectum developed on the periphery of a post hystero-salpingography peritoneal granuloma and a retroperitoneal sarcoma developed on the edge of a post-retrograde Thorotrast granuloma. The third death occurred suddenly, almost immediately after a cerebral ventriculography performed with Thorotrast.

Among the control population the number of deaths from liver cirrhosis (6) and especially from malignant tumours (12) is relatively much smaller than among systemically injected cases;

there were no deaths from any blood dyscrasia and none due to a locally induced granuloma (Table 3).

Because of the particular interest in the malignancies in our series we have prepared two more tables including details on malignant tumours (Table 4) and fatal blood dyscrasia (Table 5) which have caused death among the Thorotrast and control groups. However the allotted space and time for each communication does not allow us to show all the statistical tables nor to discuss all the results in detail in this communication.

Mean injected dose and mean latency period.

On Table 6 the mean injected dose of the usual Heyden Thorotrast solution and the mean latency period (between injection and death) are given for a few selected causes of death among systemically injected Thorotrast cases.

Only liver fibrosis and malignancies have been chosen for this table, since they represent the more important and severe of possible Thorotrast induced late sequelae. Local granulomata were not included, since they do not depend on the quantity of systemically injected drug, but only on the occurrence of extra-vascular spillage. The mean latency period, from injection to death, is of the order of 21 years.

It is curious to remark that the mean injected dose usually increases with the severity of the late effect, being highest for haemangioendotheliomas, liver fibrosis and acute leukaemias (Table 6). In all these causes of death the mean dose is above the general mean dose for the total systemically injected Thorotrast cases.

The latency period between administration of the drug and

death is highest for liver fibrosis and liver tumours, especially haemangioendotheliomas (almost 28 years on the average). It is interesting to see how the latency period of leukaemias (20 years) approaches that of aplastic anaemias (a little less than 24 years), which may suggest that at least some cases of aplastic anaemia could well have been acute aleukaemic leukaemias, as has been mentioned (4,5,7).

Discussion and Conclusions.

The present communication amplifies and confirms the results previously reported from the Portuguese Thorotrast series since 1965 (4,5,6,7,8).

The results indicates that Thorotrast when retained in the human body, either through systemic administration or when stopped in the tissues after local administration, is capable of inducing local fibrosis where it stays and, in some cases, after more years, malignant degeneration as well as the target organs are these containing R.E.S. cells, especially the liver and the bone marrow. Thorotrast action can also be exercised in tissues where the drug is deposited outside the blood vessels as in the case of local granulomata, developed in the place where the drug is spilled during intravascular administration and where it stays for a long period of time.

Comparison of these causes of death (local granulomata, liver fibrosis, fatal blood dyscrasias and malignant tumours) between systemically injected Thorotrast cases (2) and control pa-

(2) Only the 1.039 systemically injected Thorotrast traced cases were used for this comparison, since the all 797 control cases were systemically injected.

tients with indication of the respective prevalence rates for each condition considered in both series, is shown in Table 7. It is clear from such a comparison that the prevalence rates of the main causes of death considered as having a probability of being due to the radioactive late effects, are much higher among the Thorotrast series than among controls, even if the rates were calculated not in relation to the 1.039 cases traced but to the total 1.918 systemically injected Thorotrast cases - on the very unlikely assumption that all causes of death in the total Thorotrast population and related to Thorotrast had appeared only in the cases we were able to trace.

It is true that in such a peculiar diseased population as our series, that increases yearly by new cases and is losing some through death or disappearance, and followed up for many but a different number of years, prevalence rates are certainly insufficient. They may even be misleading when true risks of death shall be ascertained according to causes. In order to try to establish these risks with more accuracy a statistical analysis was performed (2) according to a methodology described and published by the authors in other papers (4,8). The results are summarized in Table 8. The analysis has shown that the number of deaths observed among the control population was higher than was to be

(2) by Drs. J. Pais Morais and J. Lopes Figueira, using the results ascertained until 31 December 1970⁽⁵⁾. It must be added that the results ascertained since that date do not alter the conclusions of the statistical analysis but only reinforce them, since the number of malignancies has increased proportionally more than the number of newly traced cases.

expected from the general Portuguese population, duly corrected for the peculiarities mentioned above, for the following specific causes of death (7th revision of the International Classification of Diseases) - Table 8 (a summary of three statistical tables published in another paper (5)):

- Malignant neoplasms of the larynx (A-49, of the 7th revision of I.C.D. - for both sexes together and for females.
- Malignant neoplasm of the bronchus and lung (A-50) - for both sexes together and for males.
- Malignant neoplasm of the bone (A-56) - for both sexes together and for females.
- Malignant neoplasm of all other and unspecified sites (A-57) including practically only liver tumours - for both sexes together, for males and for females.
- Leukaemia and aleukaemia (A-58) - For both sexes together, for males and for females.
- Lymphosarcoma and other neoplasms of lymphatic and haematopoietic system (A-59) - for both sexes together.
- A-45, A-50, A-52, A-54, A-56, A-57 - for both sexes together, for males and for females.
- A-45, A-50, A-52, A-54, A-56, A-59 - for both sexes together, for males and for females.
- As above, but including only the cases with histological confirmation - for both sexes together, for males and for females.
- Cirrhosis of the liver (A-105) - for both sexes together and for males.

These results reinforce those previously reported in a few papers (3,4,5,7,8) and confirm the conclusions previously drawn.

The incidence of primary liver tumours and especially of haemangioendotheliomas, is now appreciably greater than previously reported by our group. If all cases of liver tumours, including the cases without histological confirmation - accepted as liver tumours because of the striking clinical similarity with the confirmed cases - are considered, then the excess of liver malignancies among our Thorotrast series is really staggering.

The total amount of malignant tumours is also above the expected. Carcinoma of the bronchus and bone sarcomas may have the greatest interest in our series, because of the possible radiation effects of thorium and of its daughters on the lung and on the bone. The incidence of lung cancer in Thorotrast cases can be of great interest because it may provide an indication of a pure lung radiation risk, from excreted thoron, without an association of dust inhalation such as that existing among miners working with radioactive material, such as uranium (5). However, since the number of observed deaths from lung cancer (carcinoma of the bronchus) although significantly above expected (Table 8), has not increased since 1963 and when we do not know the tobacco habits of the Thorotrast population, we must consider our results as equivocal in this respect. However it seems that the increase of lung cancer among Thorotrast cases is not marked.

As for the bone tumours, of which we have only 2 confirmed cases in our Thorotrast series (of the third case no positive or negative confirmation could be obtained), our results seem to in-

dicates that the bone tissue radiation in Thorotrast cases (due primarily to alpha particles) is probably lower than in the radium cases with comparable burdens (5).

The most striking finding in our series, besides the extraordinarily high incidence of liver tumours, is the very high incidence of fatal blood dyscrasias, particularly of acute leukaemias. There is a very gross excess of leukaemias and other rapidly fatal blood dyscrasias among our Thorotrast group, while there is a total lack of such cases among the control population (Table 8). We may assume that probably most or at least some of our aplastic anaemia or fatal purpura cases, were aleukaemic forms of acute leukaemia, as the similarities of the respective clinical courses and even of the mean injected doses and mean latent periods (Table 6) suggest. We may conclude that this great excess represents in fact a radiation induced or precipitated condition or group of conditions.

Such results are qualitatively similar to those from other Thorotrast series, namely the Danish group (lead by Prof. Faber), and to those reported in externally irradiated populations, such as among the therapeutically irradiated ankylosing spondylitis patients (Brown, Abbott, Lea and Doll) (5). Nevertheless our results show some differences from those reported in externally irradiated populations, such as the latent period, which for Thorotrast cases is about 20 years, which is slightly more than the double of the latent period for externally irradiated cases (5 to 7 years among the irradiated ankylosing spondylitis patients). We do not know the reason for this difference but it is probably due to the fact that the total alpha irradiation from Thorotrast and daughters has a different biological effectiveness than

X-ray irradiation and also because, while is one acts at once, that from Thorotrast is delivered rather slowly over a considerable period of time and is irregularly distributed in the R.E.S. cells of the blood forming organs, according to the peculiar metabolism of Thorotrast and its movement within the human body (3,5).

Another important difference is that the risk for individuals injected systemically Thorotrast of developing such fatal blood dyscrasias seems to be appreciably greater than the one externally irradiated individuals. While this last risk is of the order of a 6 to 8 fold increase over the "natural" risk of developing leukaemia, there is probably a 12 to 16 fold increase in risk among the Thorotrast patients - or at least among the Portuguese Thorotrast patients described in this communication (5). As we have already written in a paper prepared two years ago (5) "Thorotrast, under the conditions prevailing in our systemically injected population, represents the most potent human leukaemogen yet reported".

Two more years of follow-up and collection and analysis of results have maintained our previous opinion.

Acknowledgement.

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TABLE 1

Cases by type of drug injected and route of administration
(until 31 December 1972)

Route of administration	Thorotrast				Control drugs			
	Total	Traced	Percent of		Total	Traced	Percent of	
			traced	type of admin.			traced	type of admin.
Total up of cases	9433	1231	-	-	1090	797	49.7	-
1) Systemic route:	1066	1000	94.3	-	1090	797	49.7	-
a) cerebral angi.	1062	829	86.7	79.8	301	220	63.7	36.0
b) limb arteriogr.	205	177	86.0	17.0	315	160	50.7	12.7
c) limb phlebogr.	12	7	58.3	0.7	701	180	26.0	26.0
d) angiography	40	19	46.0	1.2	600	204	41.0	21.0
e) hysterosalping.	10	11	100.0	1.1	-	-	-	-
f) pyelogram (intra or retrograde)	3	3	100.0	0.3	-	-	-	-
2) Local inj. or instillat.	845	180	37.3	-	-	-	-	-
a) peri-neural chemos.	803	170	36.7	-	-	-	-	-
b) cerebral chemos. inj.	3	3	100.0	-	-	-	-	-
c) retrograde phlebogr.	4	4	100.0	-	-	-	-	-
d) other local (a)	0	0	100.0	-	-	-	-	-

(a) Including injections around vertebrae of the legs (2), hysterosalpingography (1), mammography (1), arteriography (1) and venitriangiography (1)

TABLE 2

Number of deaths and main causes of deaths among traced "Thorotrast" and Control cases
(until 31 December 1972)

Contrast drug used	Thorotrast			Control drugs
	Total	Systemic route	Local inj. or instill.	Systemic route
Type of administration				
Total number of traced cases	1231	1038	193	797
Total number of deaths	918	882	36	845
of which:	(100%)	(100%)	(100%)	(100%)
1) Causes not possibly related with the contrast drug	644	644	20	485
	(70.3%)	(73.2%)	(76.6%)	(60.9%)
2) Unknown cause of death	77	74	3	32
	(8.4%)	(8.3%)	(11.6%)	(3.8%)
3) Causes possibly related to "Thorotrast" side-effects (a)	177	174	3	16
	(19.3%)	(19.5%)	(11.6%)	(3.9%)

(a) Local granulomata, liver fibrosis, leukaemias and other fatal blood dyscrasias and malignant tumours (specially liver tumours) - see text and for details Table 3.

TABLE 3

Main causes of death among treated "Thioridazine" and Control cases
(until 31 December 1972)

Contrastr drug used	Thioridazine		Control drug	
	Total	Systemic route	Local (by or oral)	Systemic route
Total number of treated cases	1231	1028	182	797
Total number of deaths	819	632	36	245
Main causes of death	Local granuloma ^(a)	15	16	-
	Liver fibrosis ^(b)	24	34	-
	Malignant tumours ^(c)	112	110	2
	- on the edge of local granuloma	8	6	2
	- primary liver tumours	68	68	-
	- other malignant tumours	36	36	-
	Blood dyscrasias ^(d)	23	23	-
	- leukaemia	12	12	-
	- aplastic anaemia	8	8	-
	- other fatal blood dyscrasias	3	3	-
	Other causes of death probably related to the contrastr drug (see f)	3	2	1
	Other causes of death not possibly related with the contrastr drug	664	644	30
	Unknown causes of death	77	74	3

(a) Death resulted in these cases, all of them cervical granuloma post cerebral angiography, from asphyxia (dissection of the recurrent nerve) in 2 cases, from cholesty after resection of hepatocarcinoma in 3 cases, from spontaneous external haemorrhage after fibrinolysis in 1 case and by accident rupture of the carotid during surgical attempt for the granuloma removal. Besides these 15 deaths, in 2 other cases death was due to the development of fibrosarcoma sarcomas developed on the edge of cervical granuloma, which brings to 17 the number of cases in which a local granuloma was the more or less direct cause of death.

(b) Resulting in a clinical picture identical to that of liver carcinoma.

(c) Details of these tumours are given on Table 4. They include all secondary tumours and all tumours developed within the first 5 years after injection of the contrastr drug.

(d) Details of these cases are given in Table 5.

(e) Two authors deaths almost immediately after administration of the drug (for cerebral angiography in one case and for cerebral ventriculography in another) and a case of death after splenectomy for removal of a spleen full of Thioridazine.

TABLE 4

Type of fatal malignant tumours developed among treated "Thioridazine" and Control cases
(until 31 December 1972)

Contrastr drug used	Thioridazine		Control drug	
	Total	Systemic route	Local (by or oral)	Systemic route
Total number of treated cases	1231	1028	182	797
Total number of deaths	819	632	36	245
Total number of deaths due to malignant tumours	112	110	2	12
Main type of primary malignant tumours	1) Developed on the edge of local granuloma	8	8	2
	- cervical granuloma	8	8	2
	- hepatic nodules (not post-neo granuloma)	1	1	-
	- intra-hepatic haemangioma	1	1	-
	- retro-peritoneal (post angiography)	1	-	2
	- retroperitoneal sarcoma (post angiography)	1	-	1
	2) Liver tumours (see text)	68	68	-
	- hepatocarcinoma	15	15	-
	- fibrosarcoma (developing on the edge of local granuloma and from normal liver)	5	5	-
	- hepatocarcinoma	5	5	-
	- sarcoma	3	3	-
	- retroperitoneal (of liver, spleen and from normal liver)	3	3	-
	- epithelial hepatocarcinoma	40	40	-
	3) Other malignant tumours	36	36	12
	- carcinoma of urinary tract	4	4	-
	- carcinoma of stomach	1	1	8
	- carcinoma of esophagus	1	1	-
	- carcinoma of colon	1	1	8
	- carcinoma of prostate	1	1	-
	- carcinoma of pituitary	1	1	-
	- carcinoma of testis	5	5	2
	- carcinoma of lungs	2	2	-
	- carcinoma of thyroid	1	1	-
	- carcinoma of duodenum	5	5	-
	- carcinoma of pancreas	1	1	-
	- carcinoma of uterus	-	-	2
	- peritoneal carcinomatosis	5	5	-
	- bone tumours	5	5	-
	- pleuritic lymphomatosis	2	2	-
	- multiple myeloma	1	1	-
	- chondroma	1	1	-
	- benign disease	1	1	-

TABLE 5

Type of fatal blood dyscrasias developed among treated "Thorotrast" and Control cases
(until 31 December 1975)

Control drug used	Thorotrast			Control drugs
Type of administration	Total	Systemic cases	Local effects	Systemic cases
Total number of treated cases	123	103	19	797
Total number of deaths	818	828	38	545
Total number of deaths due to blood dyscrasias	22	23	-	-
1) Leukemia	12	12		
a) Acute leukemia	9	9		
- myeloid	2(a)	2(b)		
- monocytic	1	1		
- lymphoblastic	1	1		
b) Non acute leukemia (all myeloid)	3(b)	3(b)		
2) Aplastic anaemia	8	8		
3) Fatal "purpura"	2(c)	2(c)		
4) Other	1(d)	1(d)		

- (a) One of these was an aleukemic myeloid leukemia
(b) One of which was a sub-acute evolution. All myeloid in type
(c) Death was attributed to acute idiopathic purpura
(d) The only diagnosis concerned was "acute malignant blood disease" without hematologic transformation

TABLE 6

Mean Injested Dose and Mean Latency (based on date of the most serious
Consequences and Cause of death) among systematically injected
"Thorotrast" cases
(until 31 December 1975)

Reported Cause of Death	Mean injected Dose (of the usual "Thorotrast" solution)	Mean Latency period (between injection and death)
Liver fibrosis (all cases)	39.86 ml	22.41 years
Liver fibrosis (with histologic confirmation)	36.15 ml	26.29 years
Malignant tumours (all types)	32.01 ml	26.87 years
Liver tumours (all types)	35.02 ml	27.26 years
Probable liver tumours (without histologic confirmation)	34.41 ml	26.99 years
Hemangioendotheliomas	41.64 ml	27.64 years
Data: blood dyscrasias (all types)	23.10 ml	30.94 years
Leukemia (all types)	25.89 ml	19.86 years
Acute leukemia	26.79 ml	18.32 years
Non-acute leukemia	26.87 ml	22.67 years
Aplastic anaemia	32.89 ml	25.88 years
Total of systematically injected cases	26.58 ml	26.99 years
Total of cases whose cause of death could not possibly be related with "Thorotrast" (a)	24.63 ml	4.88 years

- (a) including all the cases who have died within the first 5 years after the "Thorotrast" injection.

TABLE V
 Comparison of the results of the 1950 and 1951 censuses
 of the population of the United States, by sex and age
 (United States, 1950)

Sex and age of the population	Total population					
	1950			1951		
	Male	Female	Total	Male	Female	Total
1. Total population	151,000,000	151,000,000	302,000,000	151,000,000	151,000,000	302,000,000
2. Under 18 years of age	50,000,000	50,000,000	100,000,000	50,000,000	50,000,000	100,000,000
3. 18 years and over	101,000,000	101,000,000	202,000,000	101,000,000	101,000,000	202,000,000
4. Under 18 years of age, by sex						
a. Male	25,000,000	25,000,000	50,000,000	25,000,000	25,000,000	50,000,000
b. Female	25,000,000	25,000,000	50,000,000	25,000,000	25,000,000	50,000,000
5. 18 years and over, by sex						
a. Male	76,000,000	76,000,000	152,000,000	76,000,000	76,000,000	152,000,000
b. Female	25,000,000	25,000,000	50,000,000	25,000,000	25,000,000	50,000,000
6. Under 18 years of age, by race and sex						
a. White	40,000,000	40,000,000	80,000,000	40,000,000	40,000,000	80,000,000
b. Negro	10,000,000	10,000,000	20,000,000	10,000,000	10,000,000	20,000,000
c. Other	5,000,000	5,000,000	10,000,000	5,000,000	5,000,000	10,000,000
7. 18 years and over, by race and sex						
a. White	70,000,000	70,000,000	140,000,000	70,000,000	70,000,000	140,000,000
b. Negro	20,000,000	20,000,000	40,000,000	20,000,000	20,000,000	40,000,000
c. Other	10,000,000	10,000,000	20,000,000	10,000,000	10,000,000	20,000,000

TABLE VI
 Comparison of the results of the 1950 and 1951 censuses
 of the population of the United States, by sex and age
 (United States, 1950)

Sex and age of the population	Total population			
	1950		1951	
	Male	Female	Male	Female
1. Total population	151,000,000	151,000,000	151,000,000	151,000,000
2. Under 18 years of age	50,000,000	50,000,000	50,000,000	50,000,000
3. 18 years and over	101,000,000	101,000,000	101,000,000	101,000,000
4. Under 18 years of age, by sex				
a. Male	25,000,000	25,000,000	25,000,000	25,000,000
b. Female	25,000,000	25,000,000	25,000,000	25,000,000
5. 18 years and over, by sex				
a. Male	76,000,000	76,000,000	76,000,000	76,000,000
b. Female	25,000,000	25,000,000	25,000,000	25,000,000
6. Under 18 years of age, by race and sex				
a. White	40,000,000	40,000,000	40,000,000	40,000,000
b. Negro	10,000,000	10,000,000	10,000,000	10,000,000
c. Other	5,000,000	5,000,000	5,000,000	5,000,000
7. 18 years and over, by race and sex				
a. White	70,000,000	70,000,000	70,000,000	70,000,000
b. Negro	20,000,000	20,000,000	20,000,000	20,000,000
c. Other	10,000,000	10,000,000	10,000,000	10,000,000

Liver Studies in the Thorotrast Patients - Laboratory and Clinical Findings (Study of 175 Cases)

by

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Abstract.

In 175 non-selected patients injected with thorium dioxide, laboratory tests and clinical studies have been done.

The clinical complaints most often are related to the gastro-intestinal pathology, mainly concerning the liver. The laboratory tests disclose a serum dysproteinemia (low albumin and increased α -2 and γ -globulin) and increased levels of alkaline phosphatase. The search for α -fetoprotein has been negative in all the 10 cases in which it has been possible to perform this test.

Among the 25 cases with histological liver examination, 11 liver tumours have been found (4 hemangioendotheliomas, 5 cholangiocarcinomas and 2 adenocarcinomas); the remaining 14 cases disclosed hepatic fibrosis.

Key-words: Thorotrast - Thorium dioxide - Hemangioendothelioma - Cholangiocarcinoma - Protein electrophoresis - Alkaline phosphatase - Alpha-fetoprotein.

This study was supported by a grant from the United States Public Health Service no EC 00068, formerly RH 00039.

Introduction.

Systemically injected Thorotrast will be deposited in the R.E.S. especially in the liver, spleen and tributary lymph nodes. The liver is an organ with multiple functions that can easily be checked by laboratory tests and also an organ accessible to histological examination through biopsy. Since Thorotrast is found in great concentration in the liver it is therefore justifiable to study the liver in the Thorotrast patients.

Material and Methods.

The non-selected patients studied were 175 in number, of which 86 were men and 89 women, with ages ranging from 22 to 87 years; the quantities of Thorotrast received went from 4 to 70 ml (but were unknown in 19 cases) and the time elapsed since reception of the drug ranged from 10 to 41 years.

The laboratory tests performed, the methods used and the normal values are listed in Table I.

In 25 cases material was available for histological examination (from 17 liver biopsies and 8 necropsies).

Clinical findings.

The Thorotrast patients often presented general dyspeptic complaints, such as flatulence dyspepsia, nausea, vomiting; some also complained of pain in the right or left upper abdomen; only in a few cases we found increased intestinal transit. Though in the majority of cases the liver is not palpable, in some cases it is enlarged and the lower edge is 2 or 3 cm below the costal margin, with a firm, smooth and painful surface.

In the 11 cases with histological examination in which the

diagnosis has been a malignant liver tumour (4 hemangioendotheliomas and 5 cholangiocarcinomas and 2 adenocarcinomas) the clinical picture was the same in all cases, with jaundice and ascites, pain in the right upper abdomen, loss of weight, weakness and loss of appetite; all the symptoms increased progressively until death occurred, always between 3 and 9 months from the onset of the symptoms.

In other 13 cases, the clinical course was in all points similar to the one just described, but the histological confirmation of the liver tumour was not available.

Table I
Laboratory Tests Performed, Methods Used and Normal Values

Test	Method	Normal values
Total serum protein	Wolfsen, Cohn, Calvery and Ichiba (with changes)	6.5-8 gm./100 ml. of serum
albumin		55 - 85%
Protein		3 - 6%
electrophoresis	Grassman and Hannig	6 - 9%
globulin		12 - 14%
		14 - 18%
Glutamic oxaloacetic transaminase (GOT)	Karmen	under 40 U/ml./min.
Glutamic pyruvic transaminase (GPT)	Wroblewski and LaDow	under 40 U/ml./min.
Alkaline phosphatase (AP)	Bodansky and Shinowara	3 - 4 U Bodansky
Serum bilirubin	Mallory and Evelyn with changes by Ducci and Watson	conjugated-less than 0.24 mg./100 ml. Total-less than 1.5mg./100ml.
Bromsulphalein	Mateer, et al.	8 - 9% of retention after 45 min.
Alphafetoprotein	Abelev (immunodiffusion)	negative

Laboratory results

The results obtained are summarized in Table II.

Table II

Times Reported for Each Laboratory Test and Per Cent of Abnormal Results

Test	Times reported	Normal	Abnormal	Per cent of abnormal results
Total serum protein	151	141	10	6.6
albumin	165	48	117	70.9
Protein electrophoresis	163	141	22	13.4
globulin	163	50	113	69.3
α_1	163	100	63	38.6
α_2	163	47	116	71.1
β				
γ				
Glutamic oxaloacetic transaminase (GOT)	146	114	32	21.9
Glutamic pyruvic transaminase (GPT)	144	127	17	11.8
Alkaline phosphatase (AP)	154	46	108	70.1
conjugated	103	80	23	22.3
Bilirubin total	106	91	15	14.1
Bromsulfalein	65	36	29	44.6
Alphafetoprotein	10	10	0	0

The greatest frequency of abnormal results was found in the protein electrophoresis, with low serum albumin (70.9%) and increased α 2 (53.3%) and γ (71.1%) serum-globulins. Increased levels of alkaline phosphatase was the more frequently found abnormality among enzymatic activities (70.1%); the transaminases showed abnormal values in only a small number of cases. Bromsulphalein was performed only in a little more than one third of the cases, but it was abnormal in 44.6 per cent of the cases; it was never performed in patients with jaundice or congestive cardiac failure.

Only recently (just in 1973) it has been possible for us to begin the search for a fetoprotein in the serum; that is why we have only 10 cases, all of them negative. Of these 10 patients, 6 had an histological examination of the liver - in 4 of those, only fibrosis was found, but the other 2 showed a malignant tumour.

Comments.

The general symptoms most often found among the Thorotrast patients concern the gastro-intestinal system. Frequent are the general non-specific symptoms such as flatulence, nausea and vomiting, but with a certain frequency we find more severe symptoms such as jaundice, ascites, pain in the right upper abdomen; this last group of symptoms has been found in every patient who presented a liver tumour, and death always occurred in a short time (3 to 9 months after the onset of symptoms).

Concerning the differences from the normal values of the laboratory test results, most evident was the serum-dysproteinemia consisting in low albumin and increased alpha 2 and gamma-

globulin values; also important has been the increasing of the alkaline phosphatase values, very high in the cases with a malignant liver tumour. The search for alphafetoprotein, in the cases in which it was possible, was always negative, even in the 2 cases with histological confirmation of a liver tumour; nevertheless this is not surprising because these 2 tumours were not hepatomas, and the hepatoma seems to be in fact the type of tumour in which the alphafetoprotein appears.

We should like to point out that the clinical and laboratory alterations presented by that group of patients are more related to the time elapsed since the reception of the drug than to the quantity received. Thus, of patients with over 25 years since injection almost all of them showed clinical and laboratory test differences, and the liver tumours of this group only appeared in patients with 29 years or more since injection.

Thanks are due to Professor Carlos Manso (Chief of the Department of Chemistry - Hospital de Santa Maria) who studied the alphafetoproteins, and to Dr. Fernando Brito Barros (assistant of the Department of Biochemistry of the Hospital de Santa Maria) who performed the laboratory tests.

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Liver Ultrastructural Findings in Patients Injected with
Thorotrast.

by

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Abstract.

Liver biopsies from patients injected with Thorotrast were examined by electron microscopy. Alterations of the mitochondria, smooth and rough endoplasmic reticulum, bile canaliculi and hypertrophic Golgi complexes were found. The presence of numerous multivesicular bodies is remarkable.

Thorotrast structure is described. Aggregates of this material were found in the Kupffer and histiocytic cells accompanied by needle like structures and surrounded by dense collagen. Thorotrast was seldom seen in the hepatocyte.

These findings were identical in all the cases and more intense in the patient injected the longest time ago.

Although stressing that the lesions are not specific, the authors suggest that they may represent an adaptative reaction to Thorotrast.

Additional key-words: liver, Thorotrast, Golgi apparatus, mitochondria, smooth endoplasmic reticulum (SER), rough (RER), lysosome, bile canaliculi.

This survey was carried out with the full support of the U.S. Public Health Service Research Grant no EC 00068, formerly grant no RH 00039 and with the cooperation of the University of Lisbon.

Introduction.

The distribution of Thorotrast and the lesions it causes in human ^{1, 7} and animal liver tissue ³ have been the subject of numerous studies in optic microscopy. However, as far as we know, ultrastructural studies are still limited to experimental work on rats ^{4, 5, 6} and have not yet been carried out on human liver tissue.

The conclusions of these experiments are contradictory. While some investigators conclude that no significant changes occur besides storage of the material ^{5, 6}, others hold that there is sufficient evidence to suggest that Thorotrast causes tissue damage and therefore presume that it is a question of dosage and interval of observation ⁴. The pathogenic mechanisms suggested have been radiation damage and foreign body action.

In our human material ⁷ we observed liver cell atrophy and necrosis of isolated cells or groups of cells including acidophilic degeneration and Mallory hyalin. These findings, the lack of ultrastructural studies of human liver biopsies, the diversity of opinions at experimental level and the possibilities afforded by the specialized nature of our research group have prompted us to carry out this work.

Material and Methods.

Liver biopsies from six patients injected with Thorotrast 40/25 years ago were examined. The material was paraffin embedded and sections stained with H.E. For electron microscopy double fixation in 3% glutaraldehyde-cacodylate and 1% OsO₄ in veronal acetate buffer was followed by dehydration and Epon embedding. Sections 1 μ thick were stained with toluidine blue⁸; adjacent

thin sections stained with uranyl-acetate and lead-citrate⁹ were studied in a Philips 300 electron microscope.

Observations.

Paraffin embedded material showed no liver cells damage apart from steatosis. Thorium dioxide was seen in augmented Kupfer cells and in macrophages in portal tracts. Fibrosis could be found in some portal tracts and surrounding efferent veins always related to Thorotrast deposits. In one case of jaundiced patient, an adenocarcinoma probably from the bile tract was detected.

The observation of thick sections by light microscopy revealed: binucleated cells, nuclear polymorphism, hypertrophic nucleoli and nuclear vesicles. Small vesicles were found in some hepatocytes either surrounding the nucleus or scattered throughout the cell. Lipofuscin granules and lipid droplets were also detected (Fig. 1). Hepatocytes with very few mitochondria at the periphery were observed. Kupffer cells some of which are packed with Thorotrast particles are augmented in number. In some areas histocytes containing the same material are surrounded by dense connective tissue.

At the ultrastructural level the nuclei show membrane indentations nuclear bodies as well as cytoplasmic invaginations containing organelles such as: lipid inclusions, ribosomes and endoplasmic reticulum (Fig.2). Many of the hepatocytes contained centrioles and microtubules.

Mitochondria vary in number, shape and size (reaching $5 \times 1.2 \mu$). Some show a less electron-dense matrix than others. The orientation of the cristae is irregular and very often occur in stacks of parallel lamellae centrally or peripherally located

in the matrix. They are often curved or annular and dilated (Fig. 3 a, b, c). Some mitochondria contain paracrystalline structures, many opaque granules and a few lipid droplets (Fig. 4 a, b). Mitochondria with myelin-like figures were sometimes found in lysosomes.

Vesicular smooth endoplasmic reticulum is increased in number with areas of tubular elements sometimes arranged in parallel arrays.

Rough endoplasmic reticulum was present in lesser quantity and dilation was irregular and in patches. In some areas of the vesicles the ribosomes are detached. There is cytoplasmic vacuolation due to dilations within the cisternae of the endoplasmic reticulum. Some show myelin-like figures. Due to this and the rupture of the vesicles this alteration is sometimes so striking that it gives the impression that the organelles are either of lamellar structure or concentric vesicular profiles.

Hypertrophic Golgi complexes composed of larger vesicles of varying sizes and elongated cisternae is the rule (Fig. 6 a). Some vesicles contain moderately electron-dense material and rod-like profiles (Fig. 6 b).

Many fat droplets and myelin-like figures occurring in or out of the lysosomes are observed.

Lamellar bile pigment deposits, enclosed in vacuoles, are observed near the Golgi apparatus and the canaliculi (Fig. 7 a).

Most of the lysosomes contain lipids of different electron density, opaque flocculent material dispersed in a fine-granular matrix, as well as myelin-like concentric systems of membranes. Some autophagic vacuoles contain ferritin only or a great variety

of organelles: mitochondria, glycogen and ribosomes. In all cases many multivesicular bodies (Fig. 8) were found. In one of the patients a few rhomboedric structures were observed. They are either free in the cytoplasm or within the lysosomes. The sizes vary between $450 \times 850 \text{ \AA}$ and $180 \times 4000 \text{ \AA}$. These structures do not contain any electron-dense material (Fig. 9).

The canaliculi show many different aspects: some appear normal with small digitiform microvilli (Fig. 7 a), others present several grades of lumen distension with either absent or oedematous and hypertrophic microvilli.

The microvilli of the intercellular space frequently present similar alterations (Fig. 7) Thorotrast was never present in the canaliculi. The junction zone was always preserved. In the space of Disse and the intercellular spaces there were bands of collagen fibers.

The endothelial cells appeared normal with very few pyknotic vesicles. Kupffer cells contained polymorphic inclusions. Inside these lysosomes there are aggregates of Thorotrast particles (Fig. 10) which are always accompanied by long needle-like structures (Fig. 11). Some Kupffer cells contained long microvilli with vacuoles (Fig. 10 a). Others show a degenerative aspect with few organelles, many vacuoles and abundant Thorotrast agglomerates (Fig. 10 b). In some areas Thorotrast and cell debris-filled macrophages appears surrounded by large bands of collagen. Thorotrast deposits are unique in appearance due to their density. They are ultimately composed of small particles ($40 - 90 \text{ \AA}$ in size), which are grouped in aggregates $1000 - 3200 \text{ \AA}$ wide, and the latter in much larger deposits of irregular shape. In three cases :

only Thorotrast deposits were found in the hepatocytes. The deposits were few often surrounded by a double membrane and composed of fine particles.

Comments.

The results of this work are limited by the fact that the material is obtained only through needle liver biopsies which means restrict area. Although all the observations were made on patients who had been injected many years ago the damages we could see were relatively recent and not the initial ones. For the same reason it is impossible to describe the stages of the circulating Thorotrast, nor is it possible to evaluate the lesions step by step from the very beginning of injections. In spite of this and taking into consideration the experimental results of other authors we believe that the explanation for the only small quantity within a few hepatocytes lays in: a) the increased phagocytic activity of Kupffer cells, b) the non observation of free Thorotrast particles in the sinusoids and c) the restricted pinocytotic activity of the hepatocytes. To this we might add the large size of the aggregates, perhaps due to the long intervals between injections and liver biopsies, and the dense bands of fibroses surrounding them. This last factor also applies to the extensive deposits of thorium dioxide in other organs, particularly the spleen, thus keeping it from re-circulation. We suggest that there is a relationship between Thorotrast particles and the needle-like structures both of which are always found together.

The results of this study are similar in some respects to those in rats reported by Grampa⁴. However, besides nuclear alterations we found that the lesions were more intense in the orga-

nelles, particularly in the smooth endoplasmic reticulum, Golgi complex and mitochondria.

The strikingly high frequencies of nuclear invaginations, hypertrophic nucleoli and membrane indentations may reflect a high nuclear activity.

Although only one patient was jaundiced all cases showed bile pigment to a greater or lesser and a large number of already described lesions of bile canaliculi. The above facts may be related to the incipient lesion of some of these organelles which have not yet reached sufficient intensity to show clinical symptoms.

Rhomboedric crystalline-like structures were only observed in the patients with carcinoma. Might there be any relationship between these structures and the patient's tumour?

In each case, all the lesions found were identical but more intense in the patient with tumour who had been injected the longest time ago. These observations are in accord with the observations already described at light microscopic level by other authors ⁶ and by ourselves ⁷.

Although all these findings are not specific we wonder whether they represent an adaptive reaction to thorium dioxide with degenerative and regenerative features.

Figures.

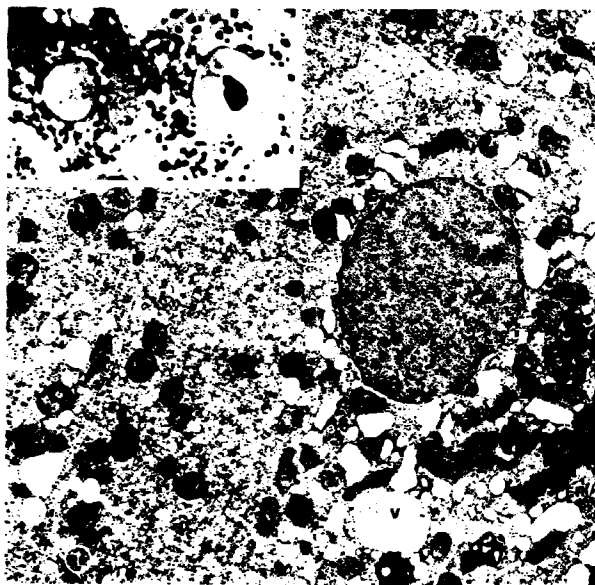
- Fig. 1** Liver cell illustrating the cytoplasmic vacuolation (V) as dilations within the cisternae of the endoplasmic reticulum (ER); lysosomes (L) x 9.000. Inset: thick section enclosing this area x 1.200.
- Fig. 2** Several hepatocyte nuclei showing cytoplasmic invaginations containing: lipid inclusions, vesicles, ribosomes and endoplasmic reticulum. a x 7.600 b x 15.200.
- Fig. 3** Liver cells with irregular mitochondria, curved and annular cristae and lamellar stacks parallel to the membrane. The matrix has low electron density. a x 36.800 b x 28.900 c x 53.900.
- Fig. 4** Enlarged cristae-dilated mitochondria with parallel filaments scattered in the matrix; the electron density of the matrix is lower than usual; granules of varying densities are also frequently observed in these organelles. x 53.900.
- Fig. 5** Dilations within the cisternae of the rough endoplasmic reticulum, containing myelin-like figures and concentric vesicular profiles appearing as lamellar structures. x 28.900.
- Fig. 6** Golgi region of active liver cells. A prominent Golgi apparatus (G) is present, composed of small vesicles and granules of varying density; rod-like profiles can be seen in some of these granules. x 23.500.
- Fig. 7** a - Peribiliary regions in hepatocytes. Bile pigment containing vacuoles (BP) and hypertrophic Golgi complex (G) x 18.700.
b - Dilated bile canaliculus. Note fibrillar material in the lumen and absence of microvilli. x 23.500.
c - Oedematous and hypertrophic microvilli in the intercellular space. x 23.500.
- Fig. 8** Liver cell with multivesicular bodies (MB) and hypertrophic smooth endoplasmic reticulum. x 9.700.
- Fig. 9** Rhomboedric crystalline-like figure (a) free in the cytoplasm (b) in lysosomes. x 53.900.
- Fig. 10** Kupffer cells (K) packed with Thorotrast aggregates (Th) a - showing degeneration x 6.000; b - Kupffer cell with long microvilli, Thorotrast deposits and vacuoles. x 8.400.
- Fig. 11** Thorotrast aggregates in lysosomes of two different Kupffer cells. Note the needle-like structures always accompanying them. x 53.900.

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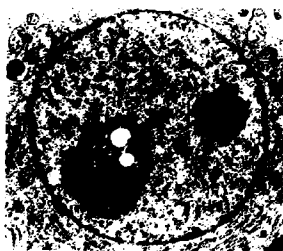
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This work was carried out in the Electron Microscopy Unit of the Faculty of Medicine of Lisbon.



1



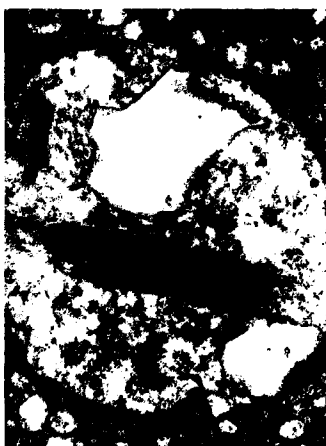
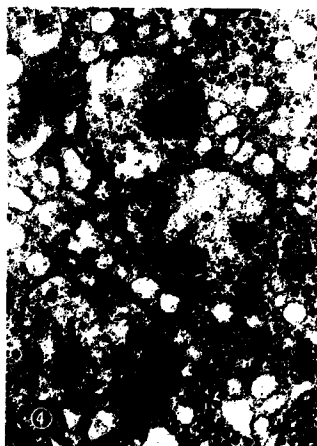
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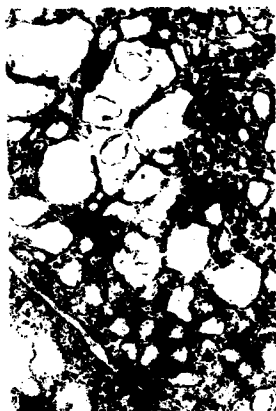
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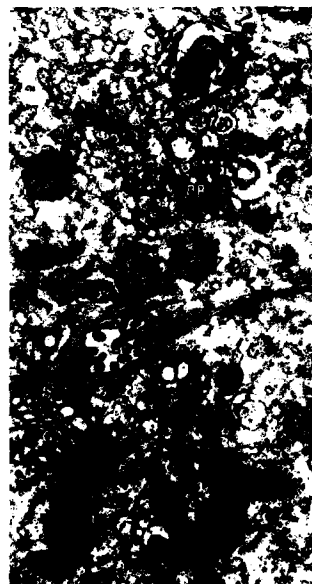
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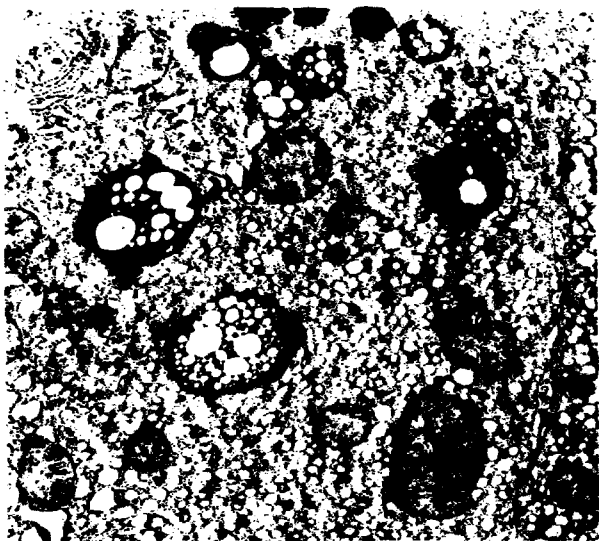
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9a



9b



10a



10b



11

Tumours developed in People injected with thorium dioxide
(Thorotrast) (Portuguese Experience)

by

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Abstract

In this paper we discuss the tumours appearing in people injected with Thorotrast: 15 cases of liver hemangioendothelioma, 1 hemangioendothelioma only of the bone-marrow, 1 reticulosarcoma, 9 cases of cholangiocarcinoma, 2 hepatomas and 5 cases of tumours on the edge of great deposits of Thorotrast. All these cases have been histologically confirmed from biopsy or autopsy. Comments are given concerning the genesis of such tumours.

Keywords: Thorotrast. Hemangioendothelioma. Cholangiocarcinoma.

This survey was carried out with the full support of the U.S. Public Health Service Research Grant no EC 00068, formerly grant no RH 00039 and with the cooperation of the University of Lisbon.

Introduction.

Since the first case of tumours appearing in people injected with Thorotrast published by Mac Mahon in 1947¹, many others have been described especially by the Scandinavian, North-American, Japanese and Portuguese authors.

Material and Methods.

The material on which our experience is based, not only of neoplasias but also of other types is shown in Table 1,

TABLE I

Total number of biopsies, autopsies and splenectomies performed
in patients injected with Thorotrast in Portugal

Time elapsed since administration of Thorotrast	Biopsies	Autopsies	Splenec- tomies
Less than 3 years	16	153	-
From 3 to 41 years	74	57	12
<u>Total</u>	90	210	12

and the 33 tumours of the reticuloendothelial organs and on the edge of thorotrastomas are shown in Table 2 and 3. The material came from biopsies and autopsies. We have performed microscopy with several methods of staining^{2,3}, in bright and dark fields, historadiography and recently electron microscopy (Philips Microscope EM 300). The results obtained have been compared with the epidemiological data⁴.

TABLE II.

Thorotrast Studies in Portugal - II. (cont.)
 TUMOURS OF THE LIVER AND OTHER RETICULOENDOTHELIAL SYSTEM ORGANS
 HISTOLOGICALLY CONFIRMED

CASE number	File number	TYPE and SITE OF TUMOUR	PROCEDURE	Volume of Thorotrast administered (ml.)	Latent period (years)
1	1100	Hemangioendothelioma of the liver	Cerebral angiography	30	3 years and 3 months
2	1003	Hemangioendothelioma of the liver	Limb arteriography	74	22
3	871	Hemangioendothelioma of the liver	Cerebral angiography	30	20
4	1000	Hemangioendothelioma of the liver	Cerebral angiography	30	20
5	836	Hemangioendothelioma of the liver	Limb arteriography	70	20
6	84	Hemangioendothelioma of the liver	Hepatosplenography	60	21
7	57	Hemangioendothelioma of the liver	Cerebral angiography	30	21
8	647	Hemangioendothelioma of the liver	Cerebral angiography	30	24
9	1040	Hemangioendothelioma of the liver	Cerebral angiography	10	27
10	720	Hemangioendothelioma of the liver (case of Prof. Tricico)	Cerebral angiography	30	20
11	33	Hemangioendothelioma of the liver (case of Dr. Campos)	Hepatosplenography	60	20
12	308	Hemangioendothelioma of the liver (Portuguese case published in Nederl. by N. Vellenga)	Cerebral angiography	40	20
13	784	Hemangioendothelioma of the liver, spleen and bone marrow	Hepatosplenography	60	27
14	21	Hemangioendothelioma of the liver and bone marrow	Cerebral angiography	30	21
15	1410	Hemangioendothelioma of the liver and several other organs (including lung metastasis)	Cerebral angiography	30	20
16	90	Hemangioendothelioma of the bone marrow	Cerebral angiography	54	24
17	91	Reticulosarcoma of the liver, spleen and bone marrow	Cerebral angiography	30	20
18	13	Cholangiocarcinoma	Hepatosplenography	70	20
19	82	Cholangiocarcinoma	Cerebral angiography	10	20
20	32	Cholangiocarcinoma	Cerebral angiography	20	20
21	1000	Cholangiocarcinoma	Cerebral angiography	30	22
22	1011	Cholangiocarcinoma	Cerebral angiography	30	22
23	2307	Cholangiocarcinoma	Limb phlebography	unknown	20
24	618	Cholangiocarcinoma	Cerebral angiography	30	24
25	814	Cholangiocarcinoma	Limb arteriography	unknown	41
26	871	Cholangiocarcinoma around liver granuloma	Cerebral angiography	30	20
27	47	Hepioma	Cerebral angiography	30	24
28	290	Hepioma	Cerebral angiography	30	22

Results concerning tumours.

I - Tumours of the reticuloendothelial organs (Table 2)

These are solitary liver tumours or more rarely multiple tumours of the liver, spleen and bone marrow or only of the liver and the bone marrow.

With the exception of one case a polymorphic reticulum cell sarcoma² all are hemangioendotheliomas and carcinomas.

Our hemangioendotheliomas have been described in detail in previous papers^{2,5,6}. Since the New York Symposium in 1966, the observed cases have in general shown the same morphology; nevertheless there is something more to add, as will be done in this paper.

The hemangioendotheliomas stem from the reticuloendothelial cells that join together in capilar structures (fig. 1) and are accompanied by the proliferation of reticular fibers. Less common is the picture of a solid tumour, but in every case there is always neoformed capilars. In the liver we can also see pictures of pure endothelioma: the endothelial cells of the sinusoids grow into the lumen, giving origin to solid images where we can find, here and there, empty spaces evidently of capillary nature. We see several blood lakes of different sizes, some of them so large that they have already been seen at the macroscopic examination during the autopsies or even when the patient was alive, through a peritoneoscope.

The tumour invades and destroys the normal structures of the organs in which it exists, but very seldom it contains Thoro-trast corpus-cules. In a few cases the capillary of the liver hemangioendothelioma invades the portal spaces (fig. 2) and the ramifications of the portal vein (fig. 3) reaching the lumen of the

mentioned ramifications and the walls of the bile canaliculi. Some liver hemangioendotheliomas cause ganglionic and pulmonary metastasis. One of the patients died from a hemoptysis resulting from the communication of blood lakes with the bronchial lumen (fig. 4) (case 15).

The other kind of tumour which developed in the liver is the hepatoma (only 2 cases, where the structure does not differ from other hepatomas in people not injected with the drug) and two types of cholangiocarcinomas: one with great glands with mucus (fig. 5), another with small glands and an extensive fibrous stroma (fig. 6). Again we practically did not find Thorotrast granules in these tumours. One grew along on the outside of the extra-hepatic biliary system with compression causing an obstructive jaundice (case 24). These glandular tumours are also the cause of metastasis in the lymph nodes of the hepatic hilum.

During the current year we have observed, during the autopsies, two cases of tumours involving both the gallbladder and the liver.

II - Tumours on the edge of great Thorotrast deposits (Table 3).

In 1967³ we have mentioned 2 spindle cell sarcomas of the neck (cerebral angiography). Our collaborator Helen Kahn published⁷ one case of cholangiocarcinoma around a liver thorotrastoma and an adenocarcinoma of the common hepatic bile duct just at the place where a thorotrastoma caused by a portography was in contact with the epithelium of the duct. There is also a fifth adenocarcinoma on the edge of a great thorotrastoma in the liver capsule, but after the necropsy, we have some doubts and think it could just as well be a carcinoma of the gall bladder which has

not been diagnosed. At last, there is a patient injected with the drug in Portugal for an hysterosalpingography which developed a carcinoma of the rectum (case published by Catel⁸).

TABLE III

TUMOURS ON THE EDGE OF GREAT DEPOSITS OF THOROTRAST
Histologically confirmed

CASE number	File Number	DIAGNOSIS	PROCEDURE	Volume of Thorotrast administered (ml)	Latent period (years)
1	87	Spindle cell sarcoma on the edge of a cervical granuloma	Cerebral angiography	14	15
2	28	Spindle cell sarcoma on the edge of a cervical granuloma	Cerebral angiography	40	20
3	871	Cholangiocarcinoma around a liver granuloma	Cerebral angiography	30	20
4	81	Cholangiocarcinoma on the edge of a granuloma of the Glisson's capsule	Cerebral angiography	20	20
5	120	Adenocarcinoma of the common hepatic duct on the edge of a post-portography granuloma	Portography	60-100	25

Comments.

Some comments have been published in 1967^{2,3,5,6} and 1968⁹.

At present we think we have sufficient data in order to group the different cases systematically.

In the first place we want to state without fear of being misunderstood, that we can speak of tumours induced by Thorotrast, and this both on the basis of morphological and epidemiological data. Very important are the comparative studies of R. Swann⁹ between man and experimental animals.

Hemangioendotheliomas - almost all of them are liver tumours, but we have one case in which 3 organs are affected, and in an-

other only the liver and the bone marrow (the patient had previously been submitted to a splenectomy). We have seen only one case in the bone marrow. Of course there are tumours with metastases. We are however convinced that the "originally multicentric hemangioendotheliomas" are more frequent than we have previously thought. The hepatic location always appeared to be the first because it practically was the basis of the clinical symptomatology with the liver as a central organ of metabolism. It is often due to a tumour at this place that death occurs through a hemoperitoneum. On the other hand, at the autopsy not every bone is cut, and sometimes no bone at all. Our conviction about the existence of multicentric hemangioendotheliomas began some time ago.

Other structures can appear, such as the ones mentioned in the excellent paper of R. Swarn⁹ that explains the names of these tumours: Kupffer cell tumours, angiosarcomas and hemangiosarcomas. We have seen such structures in our cases, but according to our opinion they only represent the polymorphism of a tumour that is essentially formed by hemangioendothelial cells.

Another problem is to know if simple hemangiomas can be related to the Thorotrast injection. We have one case like this, but statistical data do not allow us to reach any conclusion.

Liver epithelial tumours - In our series we have 11 hepatic carcinomas, but apart from 2 old cases of hepatocarcinomas (cases 27 and 28), we are now finding pure cholangiocarcinomas. Though the Japanese literature often is difficult to read, the direct contact we had with one of the Japanese authors with great experience in the matter, Miyakawa¹⁰, and what we heard in Vienna in 1965 from Tsukamoto¹¹, told us that in Japan the adenocarcinomas

have appeared first and the hemangioendotheliomas only later. In Sweden there are equal figures for hemangioendotheliomas and carcinomas (Blomberg and al.¹², Hassler and al.¹³, Dalgren¹⁴). According to R. Swann, in the United States the hemangioendotheliomas are the majority⁹.

With basis only on morphologic data, we can affirm that in the Lisbon Institute of Pathology only one case of liver hemangioendothelioma has been found in a person not injected with Thorotrast; all the other cases belong to the Thorotrast population. We think that this fact is very important in order to incriminate Thorotrast in the origin of liver hemangioendotheliomas.

We wish to call the attention to the case in which death occurred after an hemoptysis caused by lung metastases of a liver hemangioendothelioma. We had been expecting such occurrence for sometime, and it happened in our case 15.

Concerning the picture of the invasion of the structures in the periportal space by the tumour we know that it happened in a few cases. We have however never found a free communication between the tumour capillaries, open into the blood lakes and on the other side into the lumen of bile canaliculi, but we think it might be demonstrated in order to explain the melena in some people injected with the drug due to hemobilia. So far we have interpreted such cases only by the rupture of esophagic varices due to portal hypertension originating in the hepatic fibrosis).

About the liver epithelial tumours, the existence of 2 neoplasms in our series is not significant. The same can not be said about the adenocarcinomas. These adenocarcinomas came from the intrahepatic bile ducts. We think that the first type with

great glands full of mucus may come from the great ducts such as in the adenocarcinomas found in Hong Kong in people infested by the "Clonorchis Siniensis"¹⁵. These tumours are at all points similar to the Thorotrast tumours even with the presence of mucus. The second type may come from the small ducts or, according to Enriquez and col.¹⁶ (cit. Popper) from "hepatoblastos", indifferent cells capable of being the origin to hepatocytes and bile duct cells. It is true that pathologists know how rare the pure liver adenocarcinomas are. In our cases of systemic injection of Thorotrast we found a non-pure adenocarcinoma. We can not see a reason not to mention the cases of primitive liver tumours as hepatocarcinomas, cholangiocarcinomas and hepatocholangiocarcinomas, leaving the term of adenocarcinoma for practical purpose, to the carcinomas of the extra-hepatic biliary ducts and the gall-bladder, as suggested by Albertini¹⁷.

This year we have already had a patient with a tumour (glandular-type carcinoma) in which the gallbladder and the liver constituted a tumoural mass to autopsy.

It is impossible to know if a tumour from the liver invades the gallbladder or if it is the opposite. Macroscopic observation of each case can make our opinion pend to one or other side. In a second case from the current year, also an adenocarcinoma, there was only a tumour at the place of the gallbladder at autopsy. The way the cut surface looked was compatible with a liver tumour, and furthermore there was immediate contact between the tumour and a great capsular fibrous zone, with Thorotrast in great quantities on the side facing the tumour. This could be one of those cases near great Thorotrast deposits, already mentioned by R.

Swarm in his paper in Vienna⁹. It is possible that it has been a cholangiocarcinoma invading the gallbladder mainly through the lymphatics. In a paper published years ago¹⁸ we can see the importance of the lymphatic pathways through the hepatic bed of the gallbladder, mainly in the presence of liver historadiographies (fig. 17 of the paper).

Tumours on the edge of great deposits of thorium dioxide.

The tumours on the edge of Thorotrast granulomas ("Thorotrastomas"), are related to the normal structures affected. In that way the ones due to arteriography will be sarcomas as in 2 of our cases (of the neck). In the case of ascendent pyelography, in which the great deposits are near the kidney, the tumours will be carcinomas. Also of the same type are the carcinomas that appear after the installation in the peri-nasal sinuses, but we have none of these cases despite of the great number of injections performed in Portugal. This may be because a scraping of the mucosa of the sinus was performed with the removal of Thorotrast²⁰ if the contrast was retained for some days, which should signify the existence of a sinusitis.

This non-existence of tumours in such a big group of persons (177) is an indication against the carcinogenic action of the drug.

If in an ascendent pyelography the Thorotrast goes to the retroperitoneal space, the tumours that can be found will be sarcomas, as in the case of Zollinger¹⁹. One of our cases around a central thorotrastoma of the right lobe of the liver was an hepato-cholangioma, and in the case of an intra-operative attempt of portography in which the mucosae of the hepatic common duct was

affected by Thorotrast, the tumour found was an adenocarcinoma.

We may think that when Thorotrast is no longer used, these considerations have no practical interest in the sense of an extrapolation, but we have to remember that in the future the liver or some other organ may be exposed in another radiation incident.

Bone sarcomas.

In our series we have 2 cases of sarcoma, but with no histological confirmation; nevertheless the clinical picture and the radiographies are very suggestive. Recently Altner and al.²¹ published such a case with confirmation by biopsy.

Having in mind the classical work of Martland on the luminous clock-painters, we must observe whether more will appear.

Tumours of non reticuloendothelial organs.

A number of such tumours has been published isolated by other authors, but the epidemiological studies of our cases do not allow us to establish a cause-effect relationship.

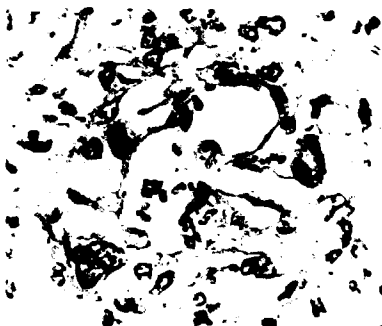
Legends of figures.

- Fig. 1 Liver hemangioendothelioma.
- Fig. 2 Liver hemangioendothelioma. Invasion of the wall of a portal ramification.
- Fig. 3 Liver hemangioendothelioma. Neoplastic thrombosis of a portal ramification.
- Fig. 4 Low magnification. Lung metastasis of a liver hemangioendothelioma. Death caused by hemoptysis.
- Fig. 5 Cholangiocarcinoma. Great glands with mucus.
- Fig. 6 Cholangiocarcinoma of small glands and much stroma.

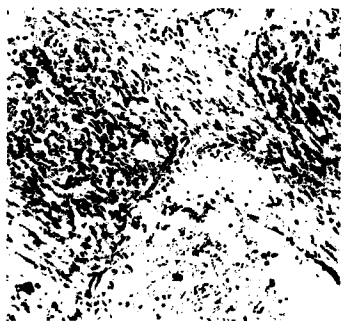
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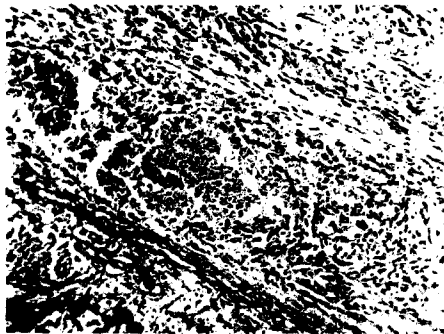
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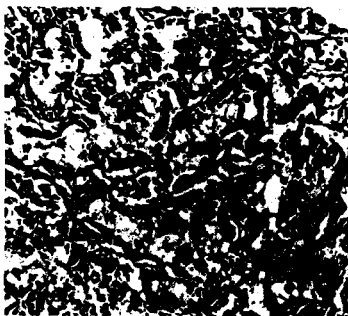
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Pathological findings in the RES (liver, spleen, lymph nodes, bone marrow) of thorotrast patients (histological and autoradiographic investigations)

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Abstract

A report is given about pathological and autoradiographical investigations of 17 patients, who received intravascularly unknown quantities of thorotrast. Different late lesions had originated: Fibrosis of the liver in 7 cases, cirrhosis of the liver in 10 cases, hemangiosarcoma of the liver in 6 cases, cholangiocarcinoma and hepatocellular carcinoma in 3 cases respectively, fibrosis and atrophy of the spleen in 15 cases, benign hemangioma of the spleen in 1 case, fibrosis and atrophy of the lymph nodes near the porta of the liver in all cases, thorotrastoma in 6 cases.

13 patients died from complications of thorotrastosis: coma hepaticum, exsanguination, cancerous cachexia and hemorrhagic diathesis. 4 patients died from peptic ulcer, heart insufficiency, heart infarction and embolism. In lymph nodes, bone marrow and thorotrastomas no tumors had developed.

There are only hypothetical ideas to explain the different tumor rates in the liver, and all other organs of the RES:

- a) Different self-absorption of alpha-rays in the liver in contrast to that of the spleen, lymph nodes and thorotrastoma.
- b) Spreading of thorotrast over a greater area in the liver than in lymph nodes and spleen.
- c) Necrosis of tumor cells in lymph nodes, thorotrastoma and spleen by the same radiation by which they had become malignant.

I would like to report about pathological and autoradiographical investigations and their results which we obtained during the past 4 years.

We examined 17 deceased patients - 14 men and 3 women - between 46 - 72 years old who partly received several injections of thorotrast during 1939 and 1945 and who died 24 - 30 years later. Injections of thorotrast were given because of injuries of arteries in 6 cases, artery occlusion in 2 cases, arterio venous aneurysm, brain embolism, brain tumor and epilepsy in 1 case respectively. In 5 cases the reason for the injection maintained obscure. All patients received intravascularly unknown quantities of thorotrast (fig. 1).

770 specimens of all parenchymal organs and numerous other tissues have been analysed histologically and autoradiographically. The content of thorium-232 was determined in 2.500 specimens of the same parenchymal organs and tissues by means

of neutron activation analysis. Dr. WESCH told you about these quantitative investigations and I shall refer myself to those data. Different late lesions had originated in the organs after a range of latency period from 24 - 30 years: The livers of the 17 patients showed fibrosis in 7 cases, cirrhosis in 10, malignant tumors in 12 cases, that is to say: 6 hemangiosarcomas, 3 cholangiocarcinomas and 3 hepatocellular carcinomas (fig.2).

The livers with fibrosis and cirrhosis are shrunken and firm and in most cases of human thorotrastosis you are macroscopically unable to decide which of the two processes is in progress just in moment.

Fibrosis of the liver means hyperplasia of fibroblasts and collagenous fibers, first of all in the periportal region and to a much lower proportion in the lobules of the liver. But shape and architecture of the Glisson's trigons and of the lobules are preserved. Thorotrast is dispersed as fine granules principally in the periportal regions but also in the liver cells, the Kupffer cells and in the macrophages of the Glisson's trigons. Fibrosis may proceed in the direction of cirrhosis at any time (fig.3).

Cirrhosis however means degeneration and regeneration of liver cells combined with fibrosis and inflammation. The limiting membranes of the lobules against the periportal regions are broken up and pseudolobules are formed. By these processes the special structure of the liver is destroyed, the vascular system is altered and followed by portal hypertension with all its consequences (fig. 4a and 4b).

Thorotrast is also irregularly dispersed as fine granules in hepatocytes, in Kupffer cells, in macrophages and between the collagenous fibers. It is not yet clear why some patients develop fibrosis and others cirrhosis despite of an identical latency period. Possibly it depends on the amount of thorotrast injected.

Hemangiosarcomas are spongy congested tumors which diffusely infiltrate the liver.

The stem cells of these tumors are the Kupffer cells. They partly grow network-like and build up partly thin blood vessels of different size. Big parts may undergo necrosis (fig. 5).

Thorotrast is usually deposited in very small amounts in the center of the tumor in greater amounts at the margin.

Cholangiocellular and hepatocellular carcinomas mostly are solid and limited tumors, developing uninodularly seldom multinodularly.

Both tumors infiltrate and destroy the liver and metastasize into the lymph nodes at the porta of the liver. Both neoplasms contain more thorotrast at the margin than in the center as already shown in hemangiosarcomas. But the absolute quantity of contrast medium is larger in the center of the carcinomas than in hemangiosarcomas.

One cholangiocarcinoma showed erythrocytes in the lumina of the tubules. That means that the tumor had invaded blood vessels by using the basal membranes of capillaries as a "guide rail" (fig.6).

The surgeons were highly astonished about this diagnosis because the tumor had looked arteriographically like an hemangioma.

In trying to interpret these results and correlate them with the data of neutron activation analysis I think the following may be stated:

1. There is no specific late lesion in the liver of thorotrast patients. Late lesions extend from fibrosis to different tumors.

2. Different late lesions may depend on different amounts of thorotrast injected, different distribution of thorotrast in the liver as demonstrated by Dr. WESCH, former or later diseases of the liver, for instance hepatitis.
3. The observation that tumors of the liver may develop multi-nodularly corresponds to the irregular distribution of thorium-232 in the organ with numerous "hot spots" of very high concentration.
4. Probably liver tumors in some cases do not develop directly by the action of thorotrast but indirectly by the way of cirrhosis, because we know that cirrhosis of the liver without thorotrast is accompanied by primary liver cell carcinoma in 15%.
In the cases with hemangiosarcoma however the action of thorotrast is probably responsible for the development of the tumor because hemangiosarcomas are very rare spontaneously developing tumors in patients with cirrhosis.

Late lesions of the spleen are fibrosis and atrophy or dystrophy. Only in one case we observed a benign hemangioendothelioma, in a second case a malignant one. But probably the latter was a metastase of a hemangiosarcoma of the liver. Lymph nodes develop fibrosis in all cases. We never saw any kind of lymphatic tumor or system disease.

In 6 cases parts of the contrast medium had been injected perivascularly. Consequently a thorotrastoma developed but no tumor (fig.7).

Fibrosis of the spleen is mainly seen around the trabecula. Thorotrast accumulates here and the particles form compact islets. Therefore self-absorption of alpha-rays is much higher that is to say much fewer cells are exposed to rays than in the liver. In my opinion this is one important factor for the very small splenic tumor rate (fig.8).

The intima cells proliferate and produce fibers narrowing the lumen of trabecular arteries. Arterial-stenosis, consecutive inadequate circulation and fibrosis lead to strong atrophy of the spleen. The organ weighs only about 20 - 30 gr compared to the normal weight of 120 - 130 gr.

In the case with benign hemangioma thorotrast was scattered in small spots around lakes of blood in the red pulp. Otherwise the contrast medium was deposited in low amounts in the intercellular spaces of the reticulum without any vital reaction.

I told you a short time ago that lymph nodes of all cases had developed fibrosis as late lesion. This is not quite correct. Properly speaking we observed two different pictures: Small quantities of thorotrast form small intercellular deposits in the reticulum without any reaction of cells or fibers. We found this way of deposition in lymph nodes of the neck, of the hilus of lungs, of the pelvis and along the arteriae femorales, that is to say in lymph nodes far away from the porta of the liver (fig. 9).

On the other hand the parapancreatic lymph nodes and the lymph nodes at the hilus of the liver and along the way of a paravasate contain many particles with marked fibrosis around them.

The fibrosis is accompanied by dystrophy and atrophy of the reticulum and destruction of the follicles and their germinal centres. Dr. WESCH has told you, that the lymph nodes near by liver, pancreas and spleen often contain more thorotrast per gram tissue weight than areas of the highest concentration in the liver. Nevertheless no neoplastic lesion or system disease had developed in one of the 78 investigated lymph nodes.

As in the spleen self absorption is high in those fibrotic lymph nodes and therefore the possibility of tumor formation is low (fig. 10).

The same reflections are applicable to thorotrastomas in the surrounding of which a marked fibrosis had developed. The influence of thorotrast as a foreign body is impressing in the thorotrastoma suggested by the foreign body giant cells. It is remarkable that none of the 17 patients showed any tumor or system disease in the bone marrow. Particles of thorotrast are deposited here intra- and intercellularly without any reaction in the reticulum as in the red pulp of the spleen. In areas with hematopoiesis - for instance in vertebral bodies - we observed in some cases activation that means hyperplasia of stemm cells.

In all other organs and tissues of the 17 patients we did not find any late lesion near the small deposits of thorotrast.

One remark as to the main cause of death:

13 patients died from direct or indirect complications of thorotrastosis: from

coma hepaticum, from

exsanguination from hemangioma or oesophageal piles

from cancerous cachexia or hemorrhagic diathesis.

4 patients died from complications which had nothing to do with thorotrastosis: from peptic ulcer, heart insufficiency heart infarction and embolism (fig. 11).

Investigations are lacking how different late lesions come about despite of identical concentrations of thorotrast.

There are only hypothetical ideas:

1. Different self-absorption in the organs of the RES may be an important factor, I discussed this.
2. It may be of importance that thorotrast spreads over a greater area in the liver than in lymph nodes and spleen. In lymph nodes and spleen radiation is concentrated on a small space. Therefore necroses recur more often and the transformation of the organ is so remarkable.

This transformation runs over a period of ten years and more in the liver. But it catches small groups of cells and is accompanied by constant regeneration.

3. Tumors are seldom in spleen, lymph nodes and thorotrastomas because those cells, which had become malignant by the radiation of thorotrast undergo necrosis by the same radiation.

If this would be true it must be true for the liver too, or one must assume, that thorotrast is constantly displaced so that there is no possibility for the discussed phenomenon.

Legends:

- Fig. 1: Data of the 17 autopsied patients.
- Fig. 2: Late lesions of the liver of the 17 patients.
- Fig. 3: Fibrosis of the liver with periportal collagenous hyperplasia but without destruction of the limiting membrane.
- Fig. 4: Cirrhosis of the liver with periportal fibrosis, inflammation and destruction of the limiting membrane.
a + b
- Fig. 5: Hemangiosarcoma of the liver with a blood vessel in the middle of the picture.
- Fig. 6: Cholangiocarcinoma with erythrocytes in the lumen of the tubule.
- Fig. 7: Late lesions in the spleen, in the lymph nodes and in thorotrastoma.
- Fig. 8: Fibrosis of the spleen with accumulation of thorotrast around the trabecula; proliferation of intima cells of an artery (middle of the picture).
- Fig. 9: Deposition of thorotrast in lymph node without vital reaction.
- Fig. 10: Fibrosis of lymph node with thorotrast in the network of the collagenous fibers.
- Fig. 11: Main cause of death of the 17 thorotrast patients.

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data of the autopsied patients	
number	17 (14♂ 3♀)
age	48-72 years
latency period	24-30 years
injection year	1929-1948
injection occasion	injury of arteries : 6 artery occlusion : 2 a.v. - aneurysm : 1 embolism : 1 brain tumor : 1 epilepsy : 1 unknown : 5
injection volume method	unknown intravascular

fig. 1

late lesions liver	17 patients
fibrosis	7 patients
cirrhosis	10 patients
tumors	12 patients malignant hemangioma 6 hepatocellular - carcinoma 3 cholangiocellular - carcinoma 3

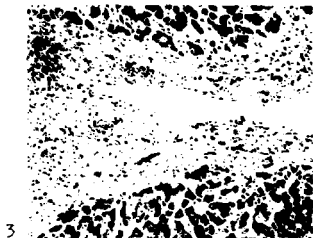
fig. 2

late lesions	fibrosis	dystrophy atrophy	tumors
spleen (15 patients)	14	12	hemangioma 1 benign 1 malignant
lymph nodes (17 patients)	17	17	-
thorotrastoma (6 patients)	6	-	-

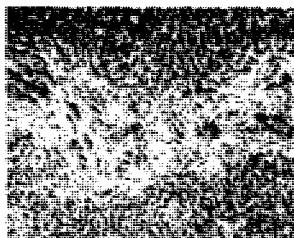
fig. 3

main cause of death 17 patients	
coma hepaticum	6
bleeding to death	4
cachexia	2
hemorrhagic diathesis	1
peptic ulcer	1
cardiac insufficiency	1
myocardial infarction	1
pulmonary embolism	1

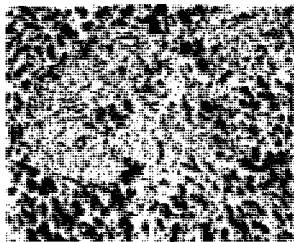
fig. 11



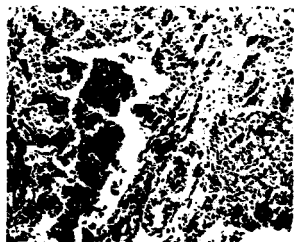
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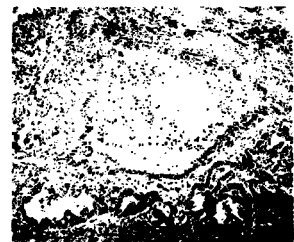
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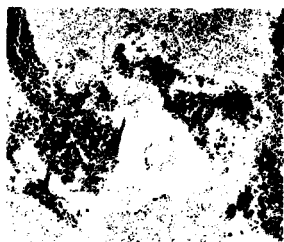
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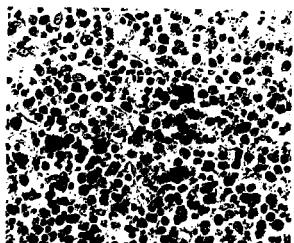
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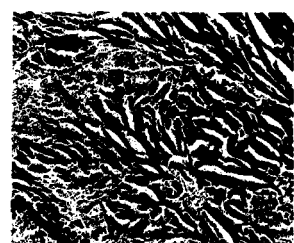
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10

Historadiographies and Autoradiographies from Pieces of Organs
of People Injected Systemically with Thorotrast.

by

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Abstract

Autoradiographies were done in organs from people injected systemically with Thorotrast. The great amount of α tracks found in the liver and the spleen in comparison to the amount existing in other organs, explains why it is in these organs, especially the liver, that the greatest number of neoplasias appear.

Historadiography has proven to be a good method to detect the thorium dioxide in the organs.

Key-words: Thorotrast - Historadiography - Autoradiography -
Tumour.

This survey was carried out with the full support of the U.S. Public Health Service Research Grant no EC 00068, formerly grant no RH 00039 and with the cooperation of the University of Lisbon.

Introduction.

The historadiographies and autoradiographies studied by us in people injected with Thorotrast have different purposes.

The historadiography is a very good method to detect the drug; it has been very useful, with small power, to allow us to evaluate the degree of fibrosis of the liver, spleen and tributary lymph nodes. Our initial work has been done with the collaboration of Jean Collete^{1,2}.

When the particles of thorium dioxide rest for a while, they induce the proliferation of fibrous tissue - of particular importance is hepatic fibrosis. We have several times published our results, in English only in the papers from the New York meeting² and the Vienna meeting^{3,4}.

The autoradiographies have been used as a control of the examination by simple light microscopy, in order to find the places where the tumours induced by Thorotrast are formed. It is a control because the results of our epidemiological studies had proved already which were the organs most susceptible to the formation of such neoplasias⁵.

Material and methods.

For historadiography we employed the extra-soft rays from 8 to 10 kV with a long exposure time (about 5 minutes). The apparatus used was a Philips BW 1009.

The autoradiographies are done from 5 μ cuts embedded in paraffin to which stripping film (Kodak AS 10) applied. The time of exposure was from 30 to 45 days. They were developed for 5 minutes in D 19 B (Kodak) and fixed with Unifix (Kodak). The observation of the cuts, stained with hematoxilin and eosin, was

made with a magnification of 400 times.

The present paper is just a preliminary note, because these studies are slow and our material great enough.

For the time being we have studied cuts from the liver (1 case), spleen (1 case), lymph nodes (1 case), pancreas (3 cases), thyroid gland (2 cases), lung (8 cases), bowel (1 case) and stomach (1 case).

Results

There is a great difference between the amount of α tracks found, on one side, in the liver and the spleen where great amounts are present and in the other organs, where they may be negative, or where only one or two tracks are seen in the whole of the slide.

In the liver the α tracks have been seen rising from the Kupffer cells or in the big scars from the histiocytes that contain the thorium present. In the spleen it is difficult to recognize the cells from which the α tracks originate because they are so numerous, but with small power we can see that they probably come from elements of the Billroth cords, from the endothelium of the sinus and from the histiocytes in the fibrous tissue.

In other organs the α tracks start from histiocytes, usually perivascular, that contain thorium. We have been especially interested in the lung, where we found α tracks in 4 of the 8 studied cases, always starting from the macrophages free within the alveoli.

Comments.

As we stated before, due to the quantity of our material and the way in which we select the organs for study, this communication is just a preliminary note. The patients we studied represent by no means a homogeneous group. Even so these samples gave us some not unexpected indications: the liver and the spleen, which have the largest number of α tracks, are the organs that present tumours in our histologically studied material. We have not yet studied any case of bone marrow but according to our experience we expect to find an important α radioactivity.

Our results, though provisional, are in accordance with the ones from K. Wegener et al.⁶. Nevertheless the reason given by these authors in order to explain the existence of a smaller number of tumours in the spleen than in the liver ("the storage of greater quantities of Thorotrast in the spleen than in the liver gives rise to a greater selfabsorption of radiation"), must be slightly corrected in face of our material. Usually when we do a histological examination of a spleen from an old case, there is practically only Thorotrast and collagen; there are no more cells left and it is impossible as we have already stated³ that tumours can be formed.

We have been particularly interested in the existence of several α tracks in the gallbladder and the lung. As shown by historadiographies¹ the lymphatic net between the liver and the hepatic bed of the gallbladder is a very rich one. Several times we found Thorotrast in the mucosae of the gallbladder from our cases. In the above mentioned paper¹ we have shown a conclusive microphoto that reproduces the Fazio's scheme⁷ in experimental works. As we have said in our first communication, during the

present year we have observed two cases of adenocarcinoma of the liver and the gallbladder that can have stemmed either from the liver with later invasion of the gallbladder, or exactly the opposite way. These cases have been to autopsy, and even during this it has not been possible for us to reach a conclusion. If they were hemangioendotheliomas, the option should be easy, but they were both adenocarcinomas.

The lungs were studied in a greater number of cases because of the interest of Professor Marinelli in the lung carcinomas in the presence of radioactive radiation. Although our epidemiological investigation did not disclose a larger number of such tumours than in normal people, it must be pointed out that in 4 or 8 cases we found α tracks, although the density of these tracks are very much inferior to the density found in the liver and the spleen. On the other hand, lung studies with the light microscope did not show any particular picture in our cases.

Legends of figures.

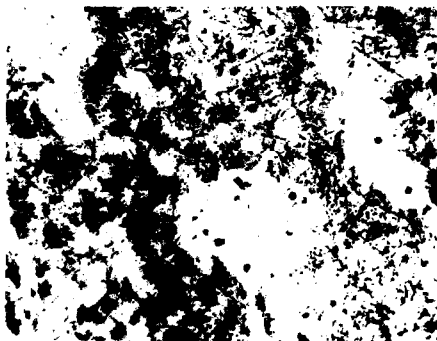
- Fig. 1 - Historadiography. Scars with Thorotrast.
- Fig. 2 - Autoradiography. Spleen. Numerous α tracks.
- Fig. 3 - Autoradiography. Liver. Numerous α tracks.
- Fig. 4 - Autoradiography. α tracks originated in the Kupffer cells with Thorotrast.
- Fig. 5 - Gallbladder. Numerous α tracks.
- Fig. 6 - Lung. α tracks originating in the alveolar macrophages.

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6

Thorotrast-induced Spindle Cell Sarcoma and Hepatic Cholangio-
carcinoma in Syrian Hamsters.

by

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Abstract

By injecting Thorotrast into the submucosa of the cheek pouch of Syrian hamsters, spindle cell sarcoma were induced at the site of injection. It was also possible to induce hepatic cholangiocarcinoma in Syrian hamsters by systemic Thorotrast administration. Both of the induced tumors were transplantable, and could also be converted into the ascitic form. In addition, the former was established as a stable strain through culture in vitro.

Histopathological and radiological examination of the tumors demonstrated that the carcinogenesis of the former proceeds from Thorotrast foreign body inflammation to Thorotrastoma formation to spindle cell sarcoma development, and that of the latter from Thorotrast deposition in the liver to adenomatous proliferation of intrahepatic bile ducts to the development of hepatic cholangiocarcinoma. In both tumors, shortening of the period from Thorotrast administration to tumor recognition was observed as the Thorotrast dose was increased. Also abnormal proliferation of alveolar epithelial cells of the lung was observed following systemic Thorotrast.

Introduction.

Thorotrast-induced human malignancies, of which a number of reports (1,2,3,4,) have been accumulated to date, may be roughly divided into those developing at Thorotrast injection sites, such as fibrosarcoma, and those resulting from systemic Thorotrast administration, such as malignant hepatic tumors.

Various animal experiments have been undertaken to study the pathogenesis of these malignancies. In experiments using mice (5), rats (6,7), rabbits (8) and guinea pigs (9), the occurrences of various malignant tumors following Thorotrast administration have been reported.

The authors (10) in their own previous animal experiments, were able to induce fibrosis of the liver, spleen and lymph nodes in mice, rats and rabbits by systemic Thorotrast administration, but failed to induce clearly recognizable malignant tumors.

In the present study, however, using Syrian hamsters as experimental material, the authors succeeded in inducing spindle cell sarcoma (11, 12) by local Thorotrast injection and hepatic cholangiocarcinoma by systemic administration. This paper describes the results obtained.

Material.

Thorotrast used in the present study was manufactured by Fellow Testagar, Inc., of the U.S.

In the local administration experiment Syrian hamsters aged 3 months with body weight ranging between 120 and 150 grams were used. In the systemic administration experiment they were aged 2 months with body weight ranging between 90 and 110 grams. In both experiments males and females were used in equal numbers.

All the animals were raised on pellet food under identical conditions.

Methods and Results.

1. Local Thorotrast Injection Experiment.

Twenty healthy Syrian hamsters were divided into four equal groups. To the animals of each group, 0.1, 0.2, 0.4 or 0.6 ml of Thorotrast was given in single injection into the submucosal soft tissue of the left cheek pouch. As controls, 20 untreated hamsters of the same kind were used.

Both the experimental animals and the controls were kept till death due to tumors or till natural death. Immediately following death, the animals were dissected for macroscopic and microscopic examinations.

Hematoxylin and eosin-staining was performed on all samples. Where deemed necessary, other staining methods were additionally employed. Further, in some cases, examination by means of electron microscopy and micro-autoradiography was conducted in conjunction with measurement of radiation dose by use of a gas-flow Geiger MILLER counter.

Development of tumors at injection sites was observed in 3 out of the 5 animals which survived more than 250 days in the experimental group given 0.1 ml of Thorotrast, in 2 out of the 4 survivals in the group given 0.2 ml, and in 2 out of the 3 survivals in the group given 0.4 ml. In the group given 0.6 ml, however, 2 animals survived over 250 days without indicating any signs of tumor development.

All told, tumors developed in 7 out of the 14 animals which survived more than 250 days. The number of controls surviving mo-

re than 250 days was 18. Tumor development was not detected in any of the latter (Table 1).

Time interval between Thorotrast injection and macroscopic recognition of tumor formation ranged from a minimum of 295 days to a maximum of 472 days. Breakdown by the amount of Thorotrast administered gave the time interval at 445 - 472 days (average 455 days, standard deviation 12.28 days) for the group given 0.1 ml, 375 - 390 days (average 383 days, standard deviation 7.48 days) for the group given 0.2 ml, and 295 - 370 days (average 288 days, standard deviation 33.63 days) for the group given 0.4 ml. Thus it was learned that increase in the amount of Thorotrast administered resulted in shortening of the injection-to-tumor recognition period. Time interval between tumor recognition to death ranged between 33 and 48 days, exhibiting little variation in relation to the amount of Thorotrast administered (Table 1).

Macroscopically, the tumors developed were mostly well-demarcated, were about the size of a walnut, and elastic-hard in consistency. On the cut surfaces, they were white-gray with yellowish central zone of necrosis. X-ray photographs revealed dot-like dense shadows in the tumors corresponding the Thorotrast granules deposited. (11).

Microscopically, the tumors consisted of interwoven bundles of long fiber-like spindle cells having ovoid or spherical nuclei with abundant chromatin, and projecting cytoplasm, which was positive by collagen and reticulum staining methods. In other words, they presented a typical image of spindle cell sarcoma of fibroblastic origin (Photo 1).

By electron micrographs, the tumor cells were shown to have centrally located ovoid nuclei and cytoplasmic processes at the cell surface, poorly developed organelles, i.e. scanty endoplasmic reticulum and ribosome granules, which lie at random in the cytoplasmic matrices. Reduced number of mitochondria and abundant intracytoplasmic fibrilles indicated the fibroblastic origin of the tumor cells (11). Metastases of these tumors were found in the lung, liver, kidney and lymph nodes.

The tumor cells could be roughly divided into those containing near diploid and tetraploid chromosome number. Homotransplantation of the tumors was made into the submucosal tissue of the cheek pouch, dorsal subcutis, peritoneal cavity, or hematogeneously via vein. The transplantation was successful in 100% of the cases. Number of cells required for successful transplantation was 3×10^6 to 1×10^3 . Successive transplantation, carried out subcutaneously and intraperitoneally also proved successful.

In intraperitoneal transplantation, the authors were able to convert the tumors into ascitic form (11). The transplantability of the tumor ascites was 100%, whether subcutaneously, intraperitoneally or hematogeneously.

Following transfer of the ascitic tumor cells to culture in vitro, a stable strain was established.

In order to examine the process of tumor-inducing by Thorotrast, changes taking place with the passage of time in the organs were examined for hamsters given 0.2 ml of Thorotrast both histopathologically and microautoradiographically for periods from 30 minutes to 15 months after Thorotrast administration.

Thirty minutes after injection, most of Thorotrast still

remained in its colloidal state and was retained by loose connective tissues of the submucosa. Thorotrast ingestion by reticulo-endothelial cells had hardly begun by this time.

Three days after injection, Thorotrast was found to have deposited in submucosal tissue as granules. Ingestion by macrophagocytes had started by this time. Congestion edema and other manifestations of foreign body inflammation were observed.

Seven days after injection, edema of submucosal tissues had disappeared, and most of the smaller Thorotrast granules had been ingested by macrophagocytes. Foreign body inflammation was found subsiding.

Thirty days to six months after injection, some of the Thorotrast ingesting cells necrosed, forming granules measuring 20 to 20 microns in diameter. The granules resulting from this intercellular Thorotrast ingestion formed closely conglomerated aggregates, over which connective tissue capsules were found developed, thus presenting a typical image of Thorotrastoma. In the subsequent period, no further changes were observed except in the cases developing malignancies. Thorotrastoma thus induced in the animals closely resembled Thorotrastoma in humans.

Incidentally, about six months after injection, translocation of Thorotrast granules to the liver, lung and spleen began in very small amounts, with deposition becoming detectable in these organs.

2. Systemic Thorotrast Administration Experiment.

Three experimental groups consisting of 10 animals each were respectively given 1.0, 1.5 and 2.5 ml of Thorotrast via injection into the sublingual vein.

The method of administration was single injection for the group given 1.0 ml of Thorotrast, two separate injections for the group given 1.5 ml, and three separate injection for the group given 2.5 ml with one week intervals. As controls, twenty hamsters of the same kind were used. In other respects, methods of experimentation and examination were the same as in the local Thorotrast injection experiment.

9 animals survived more than 150 days in the group given 1.0 ml, of those animals five developed adenomatous proliferated bile ducts in the liver and one developed hepatic cholangiocarcinoma. Among the four survival in group given 1.5 ml, three cases of adenomatous proliferation in the liver and one case of hepatic cholangiocarcinoma were recognized. In the group given 2.5 ml one of the two survivals developed adenomatous proliferation in the liver and the other developed hepatic cholangiocarcinoma.

In all, 9 cases of adenomatous proliferation in the liver and 3 cases of hepatic cholangiocarcinoma were found among the 15 animals which survived more than 150 days. It was also found that increase of the injected dose of Thorotrast was accompanied by a decrease in the number of animals surviving more than 150 days and a rise of the incidence of adenomatous proliferation in the liver and hepatic cholangiocarcinoma (Table 2).

Latent period of hepatic cholangiocarcinoma was 525 days in the group given 1.0 ml of Thorotrast, 390 days in the group given 1.5 ml and 207 days in the group given 2.5 ml. This showed that increase of the amount of Thorotrast administered resulted in remarkable shortening of the latent period (Table 2).

Macroscopically, the hepatic cholangiocarcinoma thus devel-

oped was white-grey in cut surface, measured approximately 1.5 x 1.2 cm, and were elastic-hard in consistency.

Histologically, it presented a typical image of adenocarcinoma with relatively large glandular lumens (Photo 2).

The tumor cells were atypical and varied in size, and were characterized by chromatin increase. Stroma increased was pronounced in these tumors, and large amounts of intrastromal Thorotrast deposits were observed. Metastatic foci were found in the lung, kidney and lymph nodes, giving rise to peritonitis carcinomatosa in one case.

Homotransplantation of the tumor cells was made into dorsal subcutis and peritoneal cavity. Transplantability was 100% in subcutaneous transplantation and 90% in intraperitoneal transplantation.

Successive transplantation, both intraperitoneal and hemogenous proved successful. Intraperitoneal transplantation was successful in converting solid tumors into the ascitic form.

Aiming at the examination of the process of tumor-induction, the changes taking place in the organs with lapse of time were examined by histopathological and autoradiographical methods, for periods 30 minutes to two years following injection. Thirty minutes after injection most of the Thorotrast administered still remain as colloid in the blood vessels (Photo 3). After a lapse of 24 hours following Thorotrast administration, the presence of Thorotrast in the blood stream was hardly recognizable because of ingestion by reticuloendothelial cells. Thorotrast phagocytosed by Kupffer cells of the liver and reticulum cells of the spleen was clearly in evidence. Seven days after injection, Thorotrast-ingesting cells were found to accumulate and form cell

aggregates.

Thirty days to three months after injection, these aggregates of Thorotrast-ingesting cells grew increasingly larger (Photo 4) with small round cell infiltration and collagen fiber proliferation occurring around the aggregates.

In the liver, proliferation of pseudo-bile ducts was also observed (Photo 5). After a lapse of 6 to 15 months, localized fibrosis appeared in the liver, suggesting cirrhotic changes. Adenomatous proliferation of the intrahepatic bile ducts and the development of hepatic cholangiocarcinoma were also observed (Photo 6). This cholangiocarcinoma closely resembled that occurring in humans.

In the lung, abnormal proliferation of alveolar wall cells came to be frequently observed at the deposition sites of Thorotrast granule aggregates, while in the kidney small infarctions were seen presumably attributable to embolisms due to Thorotrast granules.

Dosimetry by use of a gas-flow Geiger Müller counter indicated that a cumulative radiation dose from Thorotrast administration to occurrence of tumors were ca. 1.500~2.200 rad on average at the injection site in local Thorotrast administration and of the liver in systemic Thorotrast administration.

Discussion.

Despite the spate of reports on Thorotrast cancer-induction experiments, there has thus far been little documentation of such experiments with the Syrian hamster.

In the present study, the authors have succeeded in inducing spindle cell sarcoma by local Thorotrast injection and hepatic

cholangiocarcinoma by systematic Thorotrast administration in hamsters. The period from Thorotrast administration to tumor formation becomes shorter as the Thorotrast dose is increased.

By examining the process of tumor formation, the authors have found that in the cases locally given Thorotrast, carcinogenesis proceeds from foreign body inflammation at injection site to Thorotrastoma, thence to the development of spindle cell sarcoma. In systemic Thorotrast administration, carcinogenesis proceeds from Thorotrast deposition in the liver to adenomatous proliferation of intrahepatic bile ducts, thence to the onset of hepatic cholangiocarcinoma.

Cumulative radiation dose at injection sites or in the liver from Thorotrast injection to tumor formation was observed to ca. 1.500 - 2.200 rad on the average. As 95% of the radiation energy emitted by Thorotrast is alpha-ray energy, measurement of the dose in the area adjoining Thorotrast granules becomes of particular importance in dosimetry. According to Kato, Y. (13) the dose at the distance of the 10 micron from a large Thorotrast granule, 200 micron in diameter, is 48.000 rad/year, and that at the same distance from a medium sized Thorotrast granule, 20 microns in diameter, is 9.500 rad/year. These doses are considered to be sufficiently large to cause necrosis or atypical proliferation in Thorotrastingesting cells or adjoining cells.

Concerning other organs, alveolar wall proliferation of the lung and multiple small infarctions in the kidney following Thorotrast administration were observed but are considered specific to the Syrian hamster, as these reaction have not been obtained thus far in experimental studies using mouse, rat, rabbit or guinea pig. This specificity in the Syrian hamster may be related to the

authors previous finding (10) that Thorotrast deposition rate in the lung and kidney is greater in the Syrian hamster than in other animals.

Acknowledgement.

In concluding this work we express our sincerely thanks for advices and supports given by professor T. Wada, professor S. Hatakayama and D.Y. Nozue of Yokohama City University School of Medicine & dr. Y. Akiya and dr.N. Tamuro of Kanagawa Prefectural Medical Center for Adult Diseases, Yokohama.

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Figures.

- Fig.1. Spindle cell sarcoma with interwoven bundles of spindle cells. In the stroma a large number of Thorotrast granules.
- Fig.2. Cholangiocarcinoma of liver 13 months after i.v. Thorotrast 1.5 ml.
- Fig.3. Thorotrast as intravascular colloid 30 minutes after i.v. injection.
- Fig.4. Thorotrast in phagocytic R.E. cells in liver 1 month after i.v. injection of 1.5 ml.
- Fig.5. Multiple pseudo bile duct proliferation 6 months after i.v. Thorotrast 1.5 ml.
- Fig.6. Adenomatous proliferation in liver 10 months after i.v. Thorotrast 1.5 ml, a precarcinomatous condition?

TABLE I.

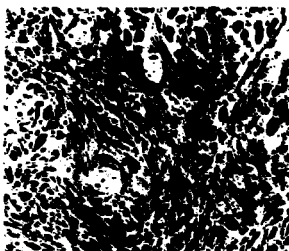
Incidence of Latent Period and Duration of Histologic Response
after subcutaneous Thorotrast Administration to Chinese Rats.

Thorotrast administered ml	No.	Survival 750 days	Incidence of adenoma	Case no.	Latent Period		Duration from resorption of tumor to death	
					Each case (days)	Average (days)	Each case (days)	Average (days)
0.1	5	5	3	A-1	445		48	
				A-2	447	455 ± 12.28	45	42.0 ± 6.08
				A-3	472		33	
0.2	5	4	2	B-1	375	385 ± 7.68	43	40.5 ± 2.46
				B-2	390		38	
0.4	5	3	2	C-1	370	388 ± 33.63	34	39.8 ± 4.38
				C-2	295		38	
				C-3	305		45	
0.6	5	2	0	0				

TABLE II.

Incidence of Latent Period of Hepatic Adenoma and Cholangiocarcinoma
after intravenous Thorotrast Administration to Chinese Rats.

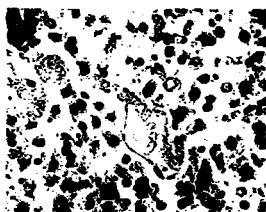
Thorotrast administered ml	No.	Survival 150 days	Incidence of adenoma	Incidence of cholangiocarcinoma	Case no.	Latent Period	
						Each case (days)	Average (days)
1.0	10	9	5	1	A-1	525	576 ± 130.3
1.5	10	4	3	1	B-1	390	
2.5	10	2	1	1	C-1	207	



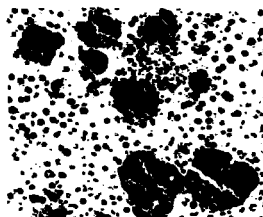
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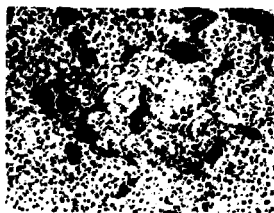
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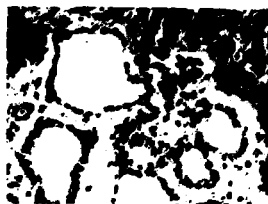
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6

Non-Radiation Effects of Thorotrast
and other Colloidal Substances

by

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Abstract

In a review of the current literature the pathogenetic effects of some non-radioactive colloidal substances in animals are presented.

The effects of these substances suggest the supposition that apart from the radioactivity other etiological factors operate in the pathogenesis of Thorotrast.

Three recent papers devoted to this special problem are quoted.

Our experimental project is designed to investigate the role of the foreign body effect present in the pathogenesis of Thorotrast.

Some ZrO_2 -aquesols were prepared according to the common peptization and condensation methods. Up to now we failed to obtain a Thorotrast like particle size distribution.

Thorotrast was produced following the method of the former manufacturer.

A possibility of the enrichment of Thorotrast by Th-230 is described.

Introduction and Review of Literature

The question whether only the radiation of Thorotrast is responsible for the long term effects after administration of the colloid, or whether the foreign body or the chemical properties are also to be taken into consideration as possible etiological factors in the tumor genesis, is discussed first by Guimares and Lamerton¹⁾.

From the chemical point of view Thorotrast should be indifferent. Bensted and Crookall²⁾, however, presume a certain chemical toxicity of Thorotrast from the result of Roth³⁾, who had observed three tumor cases in a group of 25 vineyard workers with chronic arsenic poisoning, which could not be distinguished from Thorotrast tumors. The findings of Rowley⁴⁾ that vascular injuries were presumably induced by 5-hydroxytryptamine and histamine released from damaged mast cells, also suggest the supposition that distinct pharmacological effects may be attributed to Thorotrast.

The occurrence of malignant tumors induced by other radioactive colloidal substances, however, points to the radioactivity of Thorotrast as the main etiological factor in tumor genesis.

Upton, Furth and Burnett⁵⁾ failed to observe any liver tumors in mice intravenously injected with non-radioactive colloidal gold. However, these authors were able to produce hepatomas in two groups which had received different doses of Au-198 labelled gold-sol. 2 and 5 hepatomas, respectively, of 7 and 20 animals have been recorded.

Comparable results were published by Koletsky and Gustafson⁶⁾.

On the other hand, a review of current literature indicates that these tissue reactions are not different from those of other non-radioactive macromolecular colloidal substances underlying no or little metabolic degradation and which have been parenterally administered as aquasols: Comprehensive animal experiments on the effects of solutions of some synthetic substances as polyvinylpyrrolidone (PVP), dextran, polyvinylalcohol, polymethyl- and polyethylcellulose, parenterally administered to rats, mice and rabbits were published by Hueper^{7,8)}

Although the used PVP and dextran varied in molecular

size (PVP m.w. 10 000 - 300 000; dextran m.w. 37 500 - 300 000 partly branched) the experiments failed to elicit an evident dependence of the tumor incidence on the molecular size. The tumor incidence appears to be more dependent on the animal species supported by following information. A tumor frequency of 0 - 10 % and 10 - 40 % respectively was observed in mice and rats, respectively, compared with 0,7 % in mice and 10 % in rats as controls.

The PVP induced tumors were classified according to their periodic incidence in the following groups: Reticulum-cell sarcoma of the lymph nodes, Kupffer-cell sarcoma, carcinoma of uterus, skin, ovary and breast.

Although more than 500 000 patients received PVP in the form of a 3,5 % solution (Plasmosan⁹⁾) as plasma substitut no long term effects in man have been reported in the literature so far have received.

In contrast to the findings of Hueper^{7,8)}, Haddow and Horning¹⁰⁾ did not observe any tumors after subcutaneous injection of 0,2 ml of 20 % solution of dextran into mice in weekly doses for 16 and 11 months, respectively.

Likewise no pathologic changes have been observed by Lundin¹¹⁾ after application of the Thorotrast stabilizing agent dextrin to rats. However, Rowley⁴⁾ suggested that the dextrin component is responsible for the mast cell damage and increases vascular permeability after intravenous injection of Thorotrast into rats.

Imferon and Ferrigen as dextran and dextrin stabilized sols of Fe_2O_3 should be comparable to Thorotrast concerning to their colloidal nature. The particle size of the Fe_2O_3 micelles in Imferon which was successfully used in the treatment of iron deficiency anemia is of course rather large compared with that of ThO_2 particles. Molecular weight has been determined to be as high as 180 000.

First Richmond¹²⁾ found Imferon to be carcinogenic in rats. Haddow and Horning¹⁰⁾ confirmed these results: Massive weekly repeated doses subcutaneously administered to mice and rats developed sarcomas, fibrosarcomas and histiocytomas at the site of injection.

After subcutaneous application of 0,5 ml Imferon in weekly

doses to 20 male cream hamsters, however, only one animal developed a sarcoma after latent period of 9 months. No tumors were recorded in a serie of 30 hamsters similarly treated.

Two series of 12 and 20 chinese hamsters which received doses of 0,1 and 0,3 ml Inferon, respectively, exhibited relatively high mortality due to an extraordinary high frequency of damage and hypertrophy of the liver and in some cases due to cholangiomas and hepatomas. No tumors were observed at the site of injection.

Two groups of 8 and 10 guinea pigs received 1 ml Inferon each week for 7 months. Only 5 and 3 animals survived 1 year and no tumors were recorded. Six rabbits were also injected intramuscularly, but without evident pathological effects after 16 months. Lundin¹¹⁾ generally confirmed the results by intramuscular injection of Inferon into rats with rising weekly doses over a period of 4 months (total dose: 550 or 255 mg Fe).

Ferrigen was given in the same way. The tumor occurrence in both Inferon groups and in their higher Ferrigen dose group proved to be comparable (25/27, 26/31 and 25/30 respectively tumors were recorded). However, the group treated with a lower Ferrigen dose, developed a much lower frequency of tumors of 16/31. No tumors were recorded among the controls.

In view of the high incidence of tumors at the site of injection, it is remarkable that no tumors developed in the liver or spleen before the experiments were discontinued. Lundin did not observe any proliferation of hepatic connective tissue.

Langvad¹²⁾ described the production of haemangio-endotheliomas of the liver among other tumors, such as fibrosarcomas at the site of injection in mice subcutaneously administered with Inferon. No correlation between the tumor occurrence and the injected dose became obvious.

Concerning the mechanism of the genesis of these so-called "polymer tumors" some investigators favored the view that specific chemical or physicochemical properties of these macromolecular agents (such as complex formation of macromolecular substances with proteins or the presence of impurities e.g. traces of the catalyst used in the production of these macromolecular substances) are responsible for the pathogenic process. In the opinion of other authors the tumor genesis is a non spe-

cific true foreign body effect, analogues to the sarcogenesis obtained around the various synthetic insoluble polymers and metal disks following their subcutaneous implantation. Such implantations induce the formation of granulomatous tissue of a fibrous capsule which is generally present in subcutaneous sarcomas⁸⁾. However, it is absent in the cases of experimentally induced liver tumors. Thus this subcutaneous tumor may perhaps be regarded as an example of the "Oppenheimer effect". However, it is rather difficult to invoke this mode of action in the case of liver tumors¹⁴⁾.

The problem: radiation or foreign body effects of Thorotrast was approached experimentally first by Bensted and Crookall²⁾.

These investigators injected intravenously into 18 male mice a dextrin stabilized non-radioactive ZrO_2 -sol (zirconotrast) containing 13 % w/v ZrO_2 as well as Thorotrast into 16 mice. They observed in the Thorotrast group and not well established in the zirconotrast group one haemangio-endothelioma which has been suggested by Looney¹⁵⁾ to be a Thorotrast specific tumor. The relevance of these experiments is somewhat reduced as also in 18 controls 5 liver tumors occurred. Moreover, the particle size of the used ZrO_2 -sol of 50 - 100 nm exceed that of Thorotrast by an order of magnitude (see fig. 1). In further experiments Bensted¹⁴⁾ obtained numerous vascular tumors of the spleen but not of the liver only in the Thorotrast group and not in the zirconotrast group, since this type of tumor tends to occur very late and the survival of the animals was poor in the zirconotrast group.

Mori¹⁶⁾ injected intravenously into mice, rats and rabbits different doses of Thorotrast and of the following control media: colloidal carbon as Indian ink, the diazo dye-stuff trypanblue and the Al-complex of carmine acid carmine. The both latter compounds may not be considered as true colloids. However, trypanblue is known to be firmly bound with plasma albumin being stored in the r.e.s.⁸⁾, and it is responsible for the development of reticulum-cell tumors in rats after parenteral repeated administration as a 1 % solution¹⁷⁾.

Mori¹⁶⁾ observed diffuse and rather conspicuous retrograde cellular damage of the parenchymal tissue increasing in severity according to the doses.

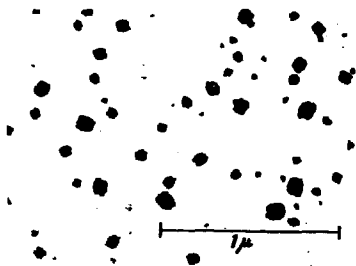


Fig.1 Electron micrograph of ZrO_2 -particles of the sol used by Bensted and Crookall

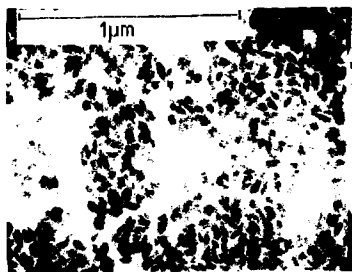


Fig.2 Electron micrograph of ZrO_2 -sol particles obtained by peptization

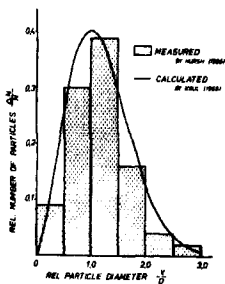


Fig.3 Particle size distribution of commercial Thorotrast

Indian ink and carmine caused only slight and temporary histological changes.

Own Experimental Project and Preliminary Results

Our experimental project considers the following time sequence studies:

- 1st, In continuation of Bensted's investigations production and application to animals of ZrO_2 - and HfO_2 -aquisols as non-radioactive colloids possessing Thorotrast like particle size distributions: studies of the biological effects of these colloids. On account of the identical chemical properties of these elements the biological effects should be similar.
 - 2nd, Production and application to animals of Zr-95 and Hf-181 labelled sols (radiozirconotrast, radiohafniotrast): studies of the distribution and retention of these radiocolloids in different organs and in the whole body and calculation of absorbed doses: comparison of biological effects due to the radiocolloids and non-radioactive colloids of zirconium and hafnium dioxide.
 - 3rd, For the same purpose a further animal group will receive Th-230 enriched Thorotrast according to the suggestion of Dudley and applied by Bensted and Faber in their hitherto unpublished works.
- Animals which will receive Thorotrast from own production and non treated animals are provided for controls.

For the production of ZrO_2 aquisols the common procedure consisting in the peptization of freshly precipitated hydroxide and the cationic condensation of Zirconyl-salts was employed. According to a dutch patent¹⁸⁾ the peptization ensues after at least 24 h cooking of the zirconium hydroxide coagulate under reflux afterwards the pH-value was adjusted to the range between 0,6 and 2 by means of conc. HCl.

Figure 2 shows the electron micrographs of the particles of the ZrO_2 -sol as obtained according to the preceding method. We failed to obtain the particle diameter distribution of 3 to 20 nm as quoted by the dutch patent and determined by x-ray diffraction, and which is comparable to that of Thorotrast (see fig. 3). Our particle diameters extend the range between

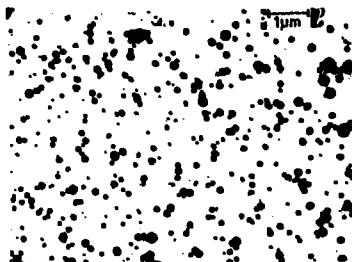


Fig.4 Electron micrograph of ZrO_2 -sol particles obtained by condensation

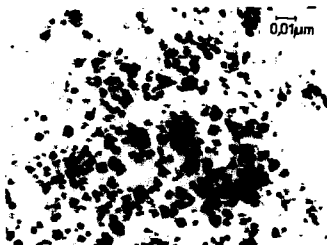


Fig.5 Electron micrograph of ThO_2 particles of commercial Thorotrast (v. Heyden Co.)

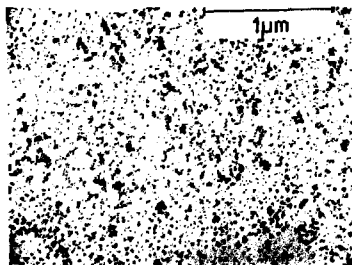


Fig.6 Electron micrograph of ThO_2 particles of Thorotrast from our own production

25 and 75 nm (see fig. 2).

The condensation of hydrolyzed ZrOCl_2 in presence of dextrin as protective colloid after successive addition of a weak basic exchange resin yielded better results with regard to the particle size distribution. The particle sizes of a sol e.g. containing as much ZrOCl_2 as equivalent to 12 % ZrO_2 cover the range of 10 to 70 nm for the diameter (see fig. 4).

Particle diameters between 3 and 7 nm should be expected if the condensation would be carried out by electrodialysis^{19,20}. These experiments are underway.

Due to the identical chemical properties of hafnium and zirconium the aquasols of hafnium dioxide can be produced by the same method.

Thorotrast has been produced according to the procedure given by the former manufacturer v. Heyden Co.²¹.

The first step is the production of a stock sol containing about 50 % ThO_2 obtained by peptization of freshly prepared ThO_2 by means of 0,2 n HCl as peptizator. The ThO_2 used has been produced by thermal decomposition of $\text{Th}(\text{C}_2\text{O}_4)_2 \cdot 6 \text{H}_2\text{O}$ at 530°C in an electric furnace. $\text{Th}(\text{C}_2\text{O}_4)_2 \cdot 6 \text{H}_2\text{O}$ was precipitated out²² of a nitric acid solution of $\text{Th}(\text{NO}_3)_4 \cdot 5 \text{H}_2\text{O}$ (p.a. quality rec. from Merck Co., Germany) by addition of oxalic acid in excess.

The concentration of the stock sol was adjusted to 37,5 % and then stabilized by successive addition of yellow dextrin (Kartoffelflocken- und Stärkefabrik eGmbH, Schrobenhausen, Germany) in portions. The pH-level of this stabilized sol was repeatedly adjusted by addition of 25 % NaOH to 8,3 since the pH-value changed after heating for half an hour at 120°C . Finally the sol was diluted to 25 % ThO_2 w/v.

The particle size distribution of the sol obtained in the described manner has proved to be in agreement with that of commercial Thorotrast (see fig. 5 and 6).

For the production of Th-230 enriched Thorotrast, Th-230 being only available as ThO_2 must be transferred into soluble form in a sodium pyrosulphate melting. The resolved melting may be precipitated as oxalate together with the calculated amount of $^{232}\text{Th}(\text{NO}_3)_4$.

In order to obtain alpha energy emission-rates being one hundred times higher than those of commercial Thorotrast an activity ratio Th-230/Th-232 of about 800 is necessary.

Acknowledgements

The authors wish to acknowledge Mr. Loose for the development of the electrodialyzer and Prof. Stolpmann for the performance of the electron microscopic examinations.

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The effect of Thorotrast enriched with Th²³⁰.

by

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Thorotrast enriched with Th²³⁰ to an α -activity 7 to 49 times normal when injected into Rabbits in a high dose (10 ml) and a low dose (0,3 ml) showed a shortened latency period for haem-angioendotheliomas compared with commercial Thorotrast, demonstrating the significance of the radiation in carcinogenesis.

The chronic irradiation delivered by Thorotrast differs from other chronic internal radiations by the fact that the source of the radiation is present as particles, and that these particles stay unchanged in the body apart from an increase in particle size with time (Guimaraes and Lamerton). This gives a possibility for two different carcinogenic mechanisms, the radiation and the particle action.

In order to permit an evaluation of the cancer mortality in Thorotrast injected patients as a pure radiation effect it is necessary to separate the action of the two carcinogens, in order to be sure that the particles only represent a minor factor in carcinogenesis. It is not possible to produce radioactivity without the granules, but a change in the specific activity of the granules should be able to give part of this information.

Such an increase could be produced by introducing a Thorium isotope into the Thorotrast and Th^{230} with a halflife of 80×10^3 years which as daughter produces Ra^{226} with a halflife of 16^{22} years would appear ideal.

Through the help of dr. Dudley, IARA, Th^{230} was procured and fresh Thorotrast was produced through the kind help of dr. Wiedemann at the Heyden Chemical Co., Munich.

The Th^{232} used was prepared from old Thorotrast. In this way the daughters released during storage would be reduced due to their adherence to the glass of the ampules in which they had been stored (Rundo). In actual fact the Thorotrast produ-

ced had an α -activity of 1/4 of the expected if the Th^{232} had been in equilibrium.

Three preparations were produced. One contained the depleted Th^{232} only. In preparation 2 Th^{230} was added to give an increase in α -activity by a factor of 7, in preparation 3 this activity was raised to a factor of 49. This was obtained by adding 1 $\mu\text{Ci Th}^{230}$ per g Th^{232} in preparation 2 and 7 $\mu\text{Ci Th}^{230}$ per g in preparation 3.

All animal experiments were performed on rabbits, and a number of experiments were visualized. A medium dose which would permit an adequate deviation in the results in a not too distant future was selected on the basis of previous rabbit experiments (Fig. 1) to be 10 ml per rabbit.

The first three experiments were performed using the depleted and the two enriched Thorium preparations in combination with a fourth using fresh commercial Thorotrast from another source. These experiments were later extended by an experiment where a dose of 0,3 ml of the most enriched Thorotrast was injected in order to study the effect of a low chemical dose - but a radiation dose comparable to the dose from control injections in the first set of experiments.

A summary of the first four experiments is given in Fig. II and Table I.

Shortly after the injections it became evident that the group 3 Thorotrast had too high an activity. The animals died during the first year of observation from liver insufficiency,

partly icteric, and with a liver which histologically showed clear signs of a radiation produced liver cirrhosis with regenerating nodules free of Thorotrast surrounded by connective tissue containing degeneration cells and with the Thorotrast in general in phagocytizing cells. The weight of the liver had decreased to approximately half the normal liver weight (Table II). The largest decrease in size was found in those animals who died first. In this group only one haemangioendothelioma developed 94 weeks after injection.

The rabbits from the three other groups showed a behaviour comparable to the previous control material. The mean age at death from tumors in group 2 was 103 days. In those injected with depleted Thorotrast the age was 147 days. The two control groups, one from the old study and the other with commercial Thorotrast showed mean ages at tumor death of 151 and 126 days. This means that the last three groups had a duration of life until death from tumor longer than was the case for the Th^{230} containing Thorotrast in group 2. It has not been possible in these experiments to demonstrate a difference between the depleted Th^{232} and the two commercial preparations. As both of these were prepared by a manufacturer different from the one preparing the experimental samples these differences may have had a number of reasons. It is known that the mode of production and the carbohydrate used to stabilize the colloid are different from the ones used in the experimental batches.

When the requirement for space in the animal house was decreasing through death of the animals the fifth experiment was started. In this only 0,3 ml Gr. 3 Thorotrast was used. The results of the experiment can be seen in Fig. III and Table III. The mean time between injection and death of tumor was found to be 249 weeks. If this should be an effect due to the effect of normal Thorotrast, it could be expected from the line drawn in Fig. I through the tumor cases produced by different Thorotrast doses that the tumors should appear some 700 to 800 weeks after injection, or after the death of the rabbit, which according to our experience should take place before 550 weeks without tumors as can be seen from the 0,6 ml experiment. If we disregard all differences in selfabsorption, differences in distribution and lack of daughter shifts etc. and only consider the absolute α -activity, the latency period could be expected to compare with the 15 ml experiment, where the mean latency is less than the 150 weeks found for the 10 ml experiment.

In actual fact the 0,3 ml enriched corresponds closely to the 4,5 ml experiment where the mean was found to be 239 weeks.

The reason for this fit to a lower Thorotrast dose can not be given. It requires a full understanding among other things of the relative change in size of the granules with time and of the differences in relative distribution of Thorium in liver and spleen, factors which are not known.

There can, however, be no doubt as to the significance of the radiation for the production of the haemangioendotheliomas in the rabbits both when high doses of Thorotrast were used and in the low dose experiment as far as the latency period of the effect is concerned. This is most marked in the low dose experiment where the decrease in latency period has brought the tumor manifestation inside the lifespan of the rabbit.

It is of course regrettable that the high dose experiment was performed with too high a dose, an effect which was made more evident because both the experimental preparation and a commercial one tended to act with latency periods shorter than the previous experiment from which the doses were estimated.

It is evident that a comparison between incidences of haemangioendotheliomas among the different groups is of no value. In the group 3 experiment the rabbits died from non-specific liver damage before a tumor could develop and in the 0,3 ml experiment as in the other long lasting experiments uterine cancer was the most common cause of death when a haemangioendothelioma was not present.

The question as to whether a theoretical non-radioactive Thorotrast might have a carcinogenic effect can not be answered through these experiments.

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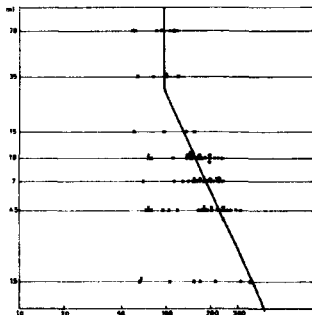
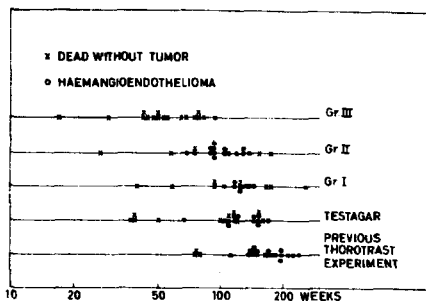


Fig. I.

Previous Rabbit experiment with commercial Thorotrast.
A curve indicating dose effect relations is placed through the mean of the experiments.



Rate of death after injection of enriched Thorotrast.

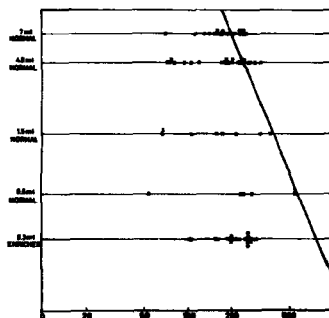


Fig. III.

Comparison of lowlevel enriched and normal Thorotrast - death rate in rabbits.

TABLE I.
The 10 ml Experiments.

Type of Thorotrast used	Tumor incidence %		Mean latency period weeks
Enriched Gr. 3	1/17	6	94
Enriched Gr. 2	15/20	75	103
Depleted Gr. 1	9/17	53	147
Testagar	12/23	52	136
Previous series	17/22	77	151

TABLE II.
Weight of Liver.

	Mean Weight g	Spread g
Gr. 1	132	59-233
Gr. 2	122	80-174
Gr. 3	66	39-114
Testagar	123	69-195
0,3 ml Gr.3	107	65-245

TABLE III.

Type of Thorotrast	Amount ml	Tumor incidence %		Latency period weeks
Normal	7	16/19	84	187
Normal	4,5	18/22	82	239
Normal	1,5	1/8	13	315
Enriched Gr. 3	0,3	13/22	59	249

The Stability of Leukemogenic Risk in Human Marrow
Irradiated by α Rays*

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Abstract

Comparison between the latent period of leukemias and the corresponding man-years at risk in the Thorotrast-injected patients of Denmark suggests that the leukemogenic risk per unit absorbed dose of chronically delivered α -radiation remains constant in time. This result is in contrast with the decline observed in leukemias induced by x radiation in therapeutically treated spondylitics.

Key Words: Thorotrast
Leukemia

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* Work performed under the auspices of the U. S. Atomic Energy Commission.

Data on irradiated spondylitics show a decline in leukemia incidence five to ten years after therapeutically administered x-ray radiation.⁽¹⁾ Atomic bomb survivors of Hiroshima and Nagasaki⁽²⁾ irradiated with a mixture of neutrons and γ rays also show a similar general trend, but the relatively small number of cases at hand precludes drawing any conclusion as to whether the decline observed in delayed leukemogenesis depends on the LET of the radiations. A preliminary test of the permanence of a leukemogenic risk induced by high LET radiation delivered at low dose rates can be made, however, by examining the results published by Faber⁽³⁾ on the epidemiology of patients injected with ThO_2 (Thorotrast) for cerebral angiography.

The test of the hypothesis proceeds as follows: Let n be the number of leukemias appearing within t years post-injection, and let \dot{D} be the average dose rate to the marrow of the population N (about 0.3 to 0.5 rads/year/cc injected). If one assumes that the number of leukemias induced per unit dose per man year at risk is constant in time, then the increment, dn , in the number of leukemia cases observed in an increment of time, dt , at the end of t years, is given by

$$dn = \epsilon \dot{D} t N dt, \quad (1)$$

where ϵ is the (constant) leukemogenic efficiency. We have taken \dot{D} to be constant with time although, per cc injected, it decreases somewhat in the first few years after injection.^(4,5) In Eq. (1) the product $N dt$ is seen to be the number of man-years at risk during dt at accumulated dose $\dot{D}t$.

Integration of Eq. (1) leads to the number of cases, $n(0, T)$, accumulated during a period from 0 to T years after injection as follows:

$$n(0, T) = \epsilon \dot{D} \int_0^T t N(t) dt. \quad (2)$$

If $N(t)$ is constant, the accumulated number of cases of leukemia would be expected to increase as the square of time after injection, since

$$n(0, T) = \epsilon \dot{D} \int_0^T t N dt = \epsilon \dot{D} N \frac{T^2}{2}. \quad (3)$$

If $N(t)$ does not vary according to some known function of time, a closed expression for $n(0, T)$ cannot be obtained. In this situation we may sum the dose man-year contributions in small intervals of time. Expressing Eq. (1) in finite steps, we have

$$\Delta n = \epsilon \dot{D} t N \Delta t$$

and

$$n(0, T) = \sum_{i=1}^m \Delta n_i = \epsilon \dot{D} \sum_{i=1}^m \bar{t}_i N_i \Delta t_i. \quad (4)$$

In Eq. (4), \bar{D}_i is the average accumulated dose in interval i , and $N_i \Delta t_i$ is the number of man-years at risk during Δt_i .

Assuming that N changes linearly during short time intervals, the appropriate value of \bar{t}_i is the time from injection to the middle of the time interval. Thus, Eq. (4) becomes

$$n(0, T) = \epsilon \bar{D} \sum_{i=1}^m \left(t_i - \frac{\Delta t_i}{2} \right) N_i \Delta t_i \quad (5)$$

A straightforward test of whether Faber's observations are consistent with the hypothesis of constant leukemogenic efficiency consists in verifying whether the following is true [from Eq. (5)]:

$$\epsilon' \propto \frac{n(0, T)}{\sum_{i=1}^m \left(t_i - \frac{\Delta t_i}{2} \right) N_i \Delta t_i} = \text{constant} \quad (6)$$

where $m = T/\Delta t$. This test has been applied to the data of Faber,⁽³⁾ excluding the man-years accumulated by patients dead (mostly of neurological diseases) within the first three years after Thorotrast injection. The latent periods of the deaths from leukemias and the number of man years at risk accruing to the total population until the death of each case are shown in the first three columns of Table 1.

TABLE 1

Leukemia in Danish Series of Thorotrast-Injected Cases.
Relationship between Number of Accumulated Cases
and Sum of Accumulated Man-Years at Risk.

n (number of leukemias)	T (latent period, yr)	$\sum_{i=1}^{T/\Delta t} \left(t_i - \frac{\Delta t_i}{2} \right) N_i \Delta t_i$	ϵ' (10^{-5})	Thorotrast injected, cc
1	8.85	27564	3.63	?
2	10.15	35649	5.61	20
3	14.1	64803	4.63	48
4	17.1	91046	4.39	50
5	19.5	123940	4.03	30
6	21.5	133540	4.49	24
7	21.8	143390(a)	4.86	?

Average 4.49 ± 0.45 a.d.

(a) This case died⁽⁶⁾ during the year following completion of the follow-up. The corresponding man-years at risk have been computed assuming that all the 475 patients alive by that date were still alive when this patient died of leukemia.

The values of t' shown in column 4 of Table 1 are indeed remarkably constant, considering the small number of leukemia cases and the long interval of time involved. Note must be taken, however, that the analysis above may be considered meaningful only insofar as the average injected dose to the patients remaining at risk remains constant with time. Although this epidemiological detail is lacking in the data, one may assume that \bar{D} cannot vary very much on the average because 76% of the population at risk has remained alive in the time interval during which all seven cases of leukemia have appeared. The influence of dose rate and total dose is strongly suggested by two observations, namely a) that the known average dose injected in leukemia cases is definitely higher (34.4 cc) than the average of all injections (23.3 cc), and b) that irrespective of the average time at risk, which is unknown for each dose category, the incidence of leukemia increases with dose as follows: 0% of the 349 cases injected with less than 20 cc, 0.26% of the 324 cases injected with 20 to 29 cc, 1.1% of the 91 cases injected with 20 to 39 cc, and 2.4% of the 84 cases known to have been injected with more than 40 cc (Faber,⁽³⁾ Tables 6 and 7). These figures are not individually significant, but the trend with dose is compelling.

It is obvious that a more precise analysis of these questions could be made if, in addition to the data submitted, additional dosimetric information were given, such as the average dose injected in patients at equal intervals of risk, and conversely, if the average time at risk were calculated for each group injected with approximately the same amount of Thorotrast. Obviously, of greatest interest would be an extension of the data already published by da Silva Horta and Cayolla da Motta,⁽⁷⁾ to include dosimetric information concerning the detailed distribution of both injected dose and man-year at risk within the injected population.

In conclusion, it may be stated that, contrary to evidence for low LET radiation (at high dose rates), the leukemogenic risk induced by α -radiation (delivered at low dose rates) can be interpreted to be a constant for intervals ranging up to more than 20 years post-injection. This result is in accord with the general radiobiological findings that there is little or no recovery from the effects produced by high LET radiation.

Acknowledgments

Many thanks are due to Dr. A. F. Stehney for very helpful discussions.

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Dose effect relations in hepatic carcinogenesis.

by

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The relative significance of radiation and physical toxicity of Thorotrast has to be solved in man. An attempt to give a risk estimate on the basis of calculated doses to the liver is presented. The results fits the published risk estimates for other types of radiation induced tumors. The procedure for the calculation of absolute risk is given. The risk is calculated to be $0.42/10^6$ "persons"/year/Rem.

The preoccupation with Thorotrast induced tumors has a number of reasons quite apart from the nosological description of a chronic toxic state.

The patients injected represent one of the largest pools of information on the effect of chronic irradiation of parenchymatous tissue with a high LET radiation.

As mentioned previously in this meeting one of the more significant problems is to what extent the toxic effect is due to the presence of Thorotrast granules and to what extent the radiation can be the cause. We have previously in animal experiments demonstrated that the radiation is of definite significance as far as the latency period of the induction is concerned and in this way probably of significance also for the rate of appearance of tumors.

It would however be of interest to study whether the information collected from a human population could contribute to this question.

If we look at the influence of the amounts of Thorotrast injected in the three types of malignancies due to Thorotrast and compare with the doses injected into non Thorotrast cancers and into the total material we get the results seen in Table I. It is evident that the number of patients with the Thorotrast dependant malignancies who have received doses in the upper reaches is higher than both in non-Thorotrast malignancies and in the general Thorotrast population. This could indicate that higher doses increase the risk for tumors, but give no quantitative guidance.

The radiation from Thorotrast contains both α - and β particles. The calculation of a correct radiation dose is however complicated by a number of other factors. Of these the selfabsorption in the Thorium dioxide granules, the shift of breakdown daughters out of the granules and their disintegration with emission of α - and β particles at other places have been thoroughly studied (Rundo (1), Kaul (2)) and can to a large extent be corrected for in the calculations. It is however at present not possible to correct for the temporary uptake of Thorium dioxide in the hepatocytes, for the perpetual shift in the place of deposition of at least part of the Thorium and for the place of final deposition in connective tissues which will then proliferate and bring the hepatocytes at least partly outside the range of the α particles.

In the further treatment of the dose dependency only the cumulative doses to the liver shall be considered. The dose has been calculated for each case taking the amount injected and the time of stay in the body into account by means of the curves for cumulative α and β doses published by Kaul (3). Patients who had died less than 7 years after the injection were excluded. - This excludes less than 30 cases and only a single case of leucemia.

The resulting cumulative doses for the different groupings in the material have been collected in Table II and the mean cumulative dose per patient has been estimated. A comparison between the groups shows some interesting differences. It was expected that the cumulative dose to the liver was lowest in the patients dying from non-cancer diseases. A somewhat high-

her mean cumulative dose was found in the patients dying from non-Thorotrast malignancies, and the highest dose was delivered in the patients dying from Thorotrast malignancies. Among these the dose was highest in the haemangi endotheliomas.

These results fit reasonably well with the picture given by the amount of Thorotrast injected into these groups.

If we however look at the dose delivered to the liver up till now in the patients still living we find that this dose is the largest of all.

This result can not be unexpected. If the distribution of injected doses in the Danish material is taken into consideration where most of the patients have received 20 ml or less, this distribution with the load on the smaller doses will in the calculations of the radiation dose tend to give much weight to the duration of the carrier state. This is also of importance when the dose to patients dead from Thorotrast cancers is considered. Due to the long latency period it has been possible for these patients to accumulate a larger radiation dose before death than if no latency period was present.

The spread of the radiation doses to the liver is in general limited when longevity is not the reason. Until further information is present the patients must be considered as having been exposed to a single mean dose only. A separation as the one which was possible in the radium carriers as described by Rowlandes et al. (4) is not possible for the Thorotrast patients.

From the results so far it is still difficult to evaluate the significance of radiation as a carcinogenic agent in this human group.

It might therefore be useful to study the risk for cancer and then to compare the risk as a dose effect relationship with what is known from other types of human radiation exposures which have recently been summarised in the U.S. National Academy of Sciences (5) report.

The risks can be calculated in a number of ways.

The risk expressed as the increase in percentage of tumors per 100 rads delivered to that organ of the patient which is under study, in this case the liver is suggested by Pochin (6).

This can be calculated on the whole of the material to be 0,88%, a figure which would correspond to the one expected from other human materials, if we take into consideration that the RBE of the predominant radiation may be up to 10.

It is however possible that a better dose-effect relationship could be obtained if only that period of time was considered when the tumors actually occurred. With an observed minimal latency period for leucemias of 5 years and for the solid tumor of 15 years a compromise at 7 years has been made which corresponds to the time when the curve for the dose to the liver flattens out and becomes horizontal. If this line is used as basis for the calculations the relative risk will rise to 1,24%, a perhaps more reasonable expression for the risk.

Both figures correspond well to the figures cited by Pochin of 0,1 - 0,5 for different types of tumor.

In the U.S. N.A.S. (5) Report three types of risk estimates are used. The simple Relative risk of $\frac{\text{obs.}}{\text{est.}}$ will for the

liver tumors give 56.

From this the % increase in relative risk per Rem can be calculated to be $\frac{55}{\text{mean dose}}$ in Rem. For the two possible mean doses this will give 1,27 and 1,80. Again these figures are in reasonable accordance with the figures cited in the Report which in most tumors and leucemias cites values below 0,20. For all cancers in the A-bomb cases, and in a number of the Radium series give higher figures.

The probably most interesting calculation in the estimate of absolute risk expressed as cases/ 10^6 persons/year/Rad. The formula generally used
$$\frac{\text{obs.} - \text{exp.} - \times 100}{\text{No of person-year} \times \text{Mean dose to tissue}}$$

The problem in the calculation will be to give a meaningful definition of the concept: person years when it is the result of a chronic irradiation which is under study. The Thorotrast patients should be well suited for such a calculation. Certain assumptions have however to be made.

It would be useful if we could make the assumption that the yearly increase in radiation induced tumors after a given acute radiation is constant when the latency period has been passed. It is doubtful whether this is the case, but for a calculation with a primary interest in orders of magnitude of effects this assumption can be considered acceptable. In the case of the Thorotrast patients this may even appear to be correct when it is considered that early and late radiation effects are manifest at the same time.

It would be of help if the dose delivered each year to the organ would be constant. In the Thorotrast cases this can be considered as fulfilled according to the dose calculations of

Kaul (3) if we disregard the first 7 - 8 years. As these years correspond to the latency period this procedure would be acceptable and would probably lead to correct estimates.

The third assumption is that the dose delivered each year can be treated as a single acute irradiation which in its effects will act without interference from the doses from other years as far as carcinogenesis is concerned. This model would appear probable but has not been proved.

If we then consider the yearly dose as the radiation unit and the cumulative number of years of observation after each such year as the person years in the formula we reach a figure of 0,42 $\frac{27,5 \times 10^6}{16.280 \times 403 \times 10}$

Again a figure of a dimension which fits well with the results obtained in other radiation induced tumors where the delivery of the radiation is acute and in a single dose.

The results of these calculations all point to one conclusion. It is with the present knowledge of dose calculations possible to reach a figure for the dose to the liver through which it is possible to correlate the effects observed in Thorotrast cases with effects seen in man after other types of ionising radiation.

The results must furthermore be taken as a strong indication that the effect of Thorotrast in man is due to the radiation and that the colloid although serious histological effects can be seen in the tissues as far as carcinogenicity is reasonably inert.

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Table I.
Relative distribution of injected
dose of Thorium dioxide solution.

Injected ml	All cases		Thorotrast tumors and leucemias		Other tumors	
	%	mean	%	mean	%	mean
5 - 9	1		0		2	
10-19	43	76	22	43	41	70
20-29	32		21		27	
30-39	8		16		7	
40-49	5	16	8	38	5	15
50	3		14		3	
unknown	8		19		15	

Table II.
Dose to liver from Thorotrast

	Sex	No.	Cumulative dose Rad	Mean dose Rad
Dead	M	107	34.655	324
without Ca.	F	67	20.629	308
	Both	174	55.284	318
Dead from Ca.	M	19	8.173	430
liver and	F	10	4.333	394
leucemia usul.	Both	29	12.506	417
Leucemia	Both	10	4.270	427
Liver Ca.	-	10	5.090	509
Hemangioma.	-	10	6.080	608
Living	M	198	121.433	607
	F	195	121.126	618
	Both	393	242.559	612
All		626	323.789	
Dose unknown		102	55.083	
Total		728	378.872	521

Aspects of Collaboration relating to Follow-up-studies

by

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Abstract

The necessity of international collaboration in order to get relevant and valid information on the thymoma carrier group is out of doubt. Some reasonable conditions must be observed. Usual statistical models are not suitable for evaluation of data obtained by follow-up-studies. Only that is the reason why the publication of original data should be recommended.

Introduction

As Dr. Faber says in the invitation paper for the present meeting: "The thymoma carrier group is slowly dying out. This state requires an international collaboration in order to get as much relevant information as possible from the study of this population." I should like to call your attention to some aspects of this important requirement.

Obvious Conditions of Collaboration

The scheme of the investigation technique must be homogene-

ous as well as the data recording system. It seems to be desirable from experience to develop a standardized basic program as small as possible, concentrated only on relevant information. In this way we are able to avoid an overwhelming influence of different physicians, different laboratory and radiological techniques in the various countries. The development of such a basic program needs further discussion, especially under the aspect: Which information is relevant? Which information is valid?

International collaboration may also be influenced by the proportion of the total number of thorotrast-administered patients, which is under investigation in the different countries. Every effort must be made to increase this proportion, where and if necessary.

All Follow-up-studies will be Cohort-studies

Although nearly essential, the assumption is unrealistic that follow-up-studies could be carried out together with one or more control-groups. You can convince a health person one time, to undergo a health-check-up of the whole body, in extreme cases twice; but you cannot hope to find populations like the Framingham one in order to perform thorotrast follow-up-studies on the international level. This fact leads directly to so called cohort- or profile studies, or, from the statistical point of view, to one sample studies over the time with implications as follows:

(i) You can test hypotheses with the respective data of the various countries only. E.g.: You can compare the incidence-rate of any given malignancy in the thorotrast-group with the incidence-rate of the respective population under the assump-

tion that the incidence-rate of the population is both a constant and a well-known parameter. However, this assumption is unrealistic very often.

(ii) If you wish to make estimations, e.g. prognostic calculations for expected tumor incidences, the question arises: What is the underlying statistical model for estimation? Usually we do assume that all elements of the sample are independent. This assumption is true, if you estimate by means of a cross-section-study. Estimations by means of follow-up-studies are dangerous, because the estimation two, four or six years later than the onset of the study are conditional estimations at best. However, the Framingham-study is a typical example, what happens, if you make estimations from an universe, which elements are not independent one from each other.

(iii) In this position we are able to use the so called life table method, either for the survival time or for the time until the first manifestation of any malignancy. However, this method depends firstly of the length of interval between two check-ups. This interval will be in practice at least two years, in terms of the life table method a very long time. Secondly, the evaluation is touched by the number of drop out-members of the cohort during any given interval. I using the life table method, considerable efforts must be made in order to keep the drop out as small as possible.

(iv) These three implications lead to the conclusion: We have to avoid all highly sophisticated statistical methods and have to observe and record only, what happens every two years with our cohorts. The need of collecting relevant and valid information is out of discussion. But in my feeling we are obliged to publish all original data, that means, to make a descriptive evaluation only.

Expected Late Effects in Thorotrast Patients *) **)

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Abstract

The paper reports the results of biophysical examinations of about 540 thorotrast patients. Measurements were made of the total-body radioactivity and of the thoron concentration in the exhaled air. Taking into account the results of special animal experiments and using the results of the direct measurements on the patients A. KAUL has calculated both the dose rate as a function of the age of the thorotrast burden and the accumulated radiation dose in different organs of the patient. The average values as well as the upper limits of the radiation exposure of the different organs (liver, spleen, marrow-free skeleton, bone marrow and lungs) are given. Using these data and the most probable values for risk coefficients published, the expected radiation induced late effects (leukaemia, bone tumours, lung tumours and liver

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**) Dedicated to Prof. Dr. B. Rajewsky on his 80th Birthday

tumours) in a thorotrast group were estimated and discussed. The results show qualitatively the importance of follow up studies of thorotrast patients for gathering optimal and useful radiobiological data.

Key words:

Thorotrast

Radiation dose

Risk coefficients

Late effects

Follow up studies

Introduction

In this paper are summarized some more or less speculative ideas concerning possible late effects to be expected in thorotrast patients.

So far it is the general opinion [1] that the following late effects of thorotrast must be taken into consideration: (1) granuloma and tumours at the site of injection; (2) tumours of the liver and (3) leukaemia; whereas the formation of: (4) lung tumours and (5) bone tumours is questionable.

Concerning the late effects of (1) and (2) and to a certain degree of (3), there is not only the effect of ionizing radiation but the effects of other factors (for example chemical and mechanical effects) which may be partially responsible for the carcinogenic properties of thorotrast [2]. Moreover, with respect to the effects of (1) and (2) there are no groups of persons with which to compare the same late effects caused by other sources of radiation and in other dose ranges. These reservations do not exist for the effects of (3), (4) and (5). The investigation of thorotrast patients may therefore -above all- provide results with respect to a relationship between the effective radiation dose and the incidence of leukaemia, lung tumours and bone tumours. At the same time it should be pointed out that a negative statement,

which means no significant increase of tumour incidence compared with the spontaneous incidence, may be as important as a positive one.

Results of Whole-Body Measurements and Estimation of the Radiation Dose in Liver, Spleen and Bone of Thorotrast Patients

The measured total body burden of ^{208}Tl of the thorotrast patients varies between about 10 nCi and about 1000 nCi. With the knowledge of the excretion rates of the different decay products of ^{232}Th the total body burden of ^{232}Th can be calculated. From the specific ^{232}Th -activity of the colloidal ThO_2 -solution then the total amount of thorotrast injected can be estimated with an accuracy of 10 - 15 % for patients without paravascular deposits and of 20 % for patients with paravascular deposits [3]. The lower limit of measured ^{208}Tl -activity of 10 nCi corresponds to an injected amount of thorotrast of about 1 ml. The upper limit of 1000 nCi corresponds to about 110 ml.

Fig. 1 gives the distribution (%) of the injected primary thorotrast solution (ml) for 534 cases. Only 11 % of the patients were injected with more than 40 ml with an average of 50 ml corresponding to a measured ^{208}Tl -activity of about 420 nCi.

For purposes of estimation of radiation dose in the different organs of interest a mean value of 15 ml thorotrast primarily injected seems to be a reasonable figure. According to the investigations of KAUL [4] [5] radiation dose rates and cumulative doses can be estimated. The calculated mean radiation doses from alpha particles in liver, spleen, bone marrow and skeleton are summarized in Table I, assuming an average of 15 ml and an upper limit of 50 ml thorotrast solution injected. The contribution of beta and gamma radiation to the total absorbed dose only amounts to between about 5 % and 10 % and can be neglected. The mean exposure time of all patients examined was 30 years. The dose rates of alpha radiation after injection of 20 ml thorotrast are in the order of 0,5 rad/week (liver), 1 rad/week (spleen) and 0,01 rad/week (skeleton) [5].

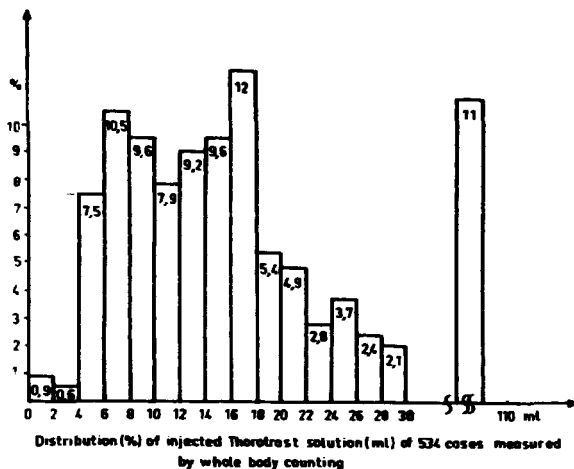


Fig. 1

TABLE I. ABSORBED DOSE IN RADS FROM ALPHA PARTICLES
IN DIFFERENT ORGANS OF THOROTRAST PATIENTS OVER A
PERIOD OF 30 YEARS

ORGAN	AVERAGE (15 ml)	UPPER LIMIT (30 ml)
LIVER	600	1300
SPLEEN	1400	3000
BONE MARROW	280	900
SKELETON	20	70

Results of Measurements of Thoron Concentration in the Exhaled Air and Estimation of the Radiation Dose Distribution in the Lungs of Thorotrast Patients

The thoron concentration of the exhaled air of each thorotrast patient was measured with a special equipment and method developed at our institute [7]. It varied between 1×10^{-10} Ci/litre and 60×10^{-10} Ci/litre. According to the procedures and results given by R. GRILLMAIER in a paper at this meeting [8] [9], the absorbed dose in the lungs of thorotrast patients from alpha particles of thoron and its short-lived daughters were estimated for an average injected amount of 15 ml and an exposure time of 30 years. The results are given in Table II.

TABLE II. EXPOSURE OF LUNGS OF THOROTRAST PATIENTS
(EXPOSURE TIME 30 YEARS AFTER A 15 ML-INJECTION OF THOROTRAST)

PART OF THE EXPOSED LUNG	ABSORBED DOSE FROM ALPHA PARTICLES (RADS)
BRONCHI	50
MAIN BRONCHI	230
TRACHEA	370

It is known that after inhalation of ^{222}Rn -decay products by uranium miners the maximum radiation exposure and the induction of lung cancer occurs in the region of the bronchi. With thorotrast patients the absorbed dose in the bronchi is only 50 rad. In comparison, the absorbed dose in the main bronchi amounts to more than 200 rad and the maximum dose of about 400 rad is in the trachea.

Expected Late Effects

Bone tumours:

The mean alpha radiation dose of marrow-free bone of thorotrast patients is about 0,7 rad per year corresponding to the absorbed alpha ray dose from about $1/4$ of the maximum permissible body burden of ^{226}Ra (0,1 μCi ^{226}Ra : 3 rad per year). The lack of any statistically significant increase in bone tumours rate of thorotrast patients relative to a suitable control group [10] may be considered as an important additional support for the maximum permissible body burden of 0,1 μCi for ^{226}Ra , as recommended by ICRP and for the corresponding limits for all other bone-seeking radionuclides related to Ra.

According to the new data reported by A. KAUL in one of his papers, read at this Meeting [11] the mean dose in marrow-free skeleton probably is higher than 0,7 rad per year (about 2 rad per year for an injected amount of 15 ml thorotrast), corresponding to $2/3$ of the alpha ray dose from 0,1 μCi ^{226}Ra . Even by taking into account these higher values, our general conclusions concerning the possible incidence of bone tumours are not changed.

The paper given by R. E. ROWLAND [12], has pointed out some new aspects of this problem by comparison with the findings of SPIESS and MAYS with ^{224}Ra -injected patients [13]. The accumulated dose from translocatable ^{224}Ra to bone surfaces of thorotrast patients estimated by ROWLAND and RUNDO is about 60 rad in 30 years for an injection level of 50 ml. It is evident that this dose is only a fraction of the mean dose of the marrow-free skeleton calculated by KAUL (about 220 rad in 30 years) [11]. We need further follow up studies of thorotrast patients to decide, whether only bone surface dose is responsible for tumour incidence.

Leukaemia:

The mean dose-equivalent of the bone marrow is about 90 rem per year (Table I) assuming a quality factor of 10 for alpha

particles. On the assumption that a single exposure of the bone marrow causes an increase of the incidence of leukaemia during the subsequent 10 years with an average increase of 2 cases of leukaemia per rem per 10^6 persons each year, the recommended value of the risk coefficient would be 20 per 10^6 man-rem [4, 15, 16, 17]. On the assumption that a continuous exposure of the bone marrow caused by thorotrast is as effective as a single whole body exposure (see [6] [7]) a mean dose-equivalent of 900 rem (exposure time 10 years) would be responsible for an increase of leukaemia incidence. That means, that about 2 additional cases of leukaemia have to occur among 1000 thorotrast patients per year. Within a follow-up time, for example of 10 years, altogether 20 cases of leukaemia among 1000 thorotrast patients would be registered compared with about one spontaneous case of leukaemia within this time. This estimated figure is in good agreement with 23 fatal blood dyscrasias from the Portuguese thorotrast population of 998, traced by SILVA HORTA, ABBATT and others [8].

Lung tumours:

The spontaneous incidence of lung tumours is $7 \cdot 10^{-4}N/\text{year}$ (where N is the number of persons). The risk coefficient for radiation-induced lung cancer generally recommended today is 10 per 10^6 man-rem [4, 15, 17]. To obtain statistically significant results the number of radiation induced lung tumours should be greater than 36 of the spontaneous incidence ($36 = \sqrt{7 \cdot 10^{-4}N}$). With a follow-up time of 10 years and an average dose equivalent of 1000 rem (Table II), the minimum number of patients that would have to be examined is about 700. Undoubtedly an increased incidence of lung cancer with thorotrast patients would be a pure radiation effect, if we do not take into consideration possible special smoking habits of the thorotrast group. However in the Portuguese population of about 1000 cases up to now no significant increase of lung tumours rate could be demonstrated (only 2 cases of carcinoma of the bronchus occurring 1 and 4 years after thorotrast injection) [9].

Liver tumours:

The spontaneous incidence is about $2 \cdot 10^{-5}$ N/year (N: number of persons). Concerning liver tumour incidence, the non radiation effects of thorotrast may be important. Nevertheless the following estimation is based on a pure radiation effect. Assuming a mean radiation dose of 2000 rem in 10 years (Table I) and a risk coefficient of 8 per rem 10^6 persons per year [5] we estimate 16 additional cases with liver tumours per 1000 patients per year compared with less than 1 spontaneous case per year. For comparison: in the Portuguese group up to now 52 liver tumours could be demonstrated [10].

For conclusion it must be pointed out, that these are very rough and speculative estimations. Many of our assumptions are problematic (for example: the generally adopted RBE-value of 10 for alpha particles, pure radiation effects, the risk coefficients used, which are mainly derived from single exposure with relative high doses).

But even these simple considerations show qualitatively the importance of follow up studies of thorotrast patients for gathering optimal and useful radiobiological data. Compared with the efforts and expenses for the recording and the first clinical and biophysical examination of the patients, the follow-up studies are relative simple (only a routine medical examination). We therefore believe that recording and first examination of the patients must be combined with systematic follow-up studies within a time of at least 10 years.

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Concluding discussion.

Professor J.S. Mitchell opened the session by giving a survey of the meeting and its results.

The meeting has been successful in bringing forward new information on practically all the points under discussion. Furthermore the papers has made it possible to place the Thorotrast study at its proper place in relation to other radioactive contaminations especially plutonium and perhaps radioactive drugs.

The dosimetry is getting better but we have now got as far as we can on a first approximation of the general dose. We must now study the effects of inhomogeneous distribution in both liver and in bone. This leads us to studies of mechanisms of action which have only been briefly touched upon. The significance of biological findings such as the cytogenic effects, the possibility of multiple tumors and of the latency period, are all fields mentioned in the presented papers. The problem of hormone action and immunology has been touched upon and even the basic problems of the cell type at risk have been discussed without a clear answer. Probably the most important points has been that we have met one another as a possible start for further collaboration, and here it is important that both WHO and IAEA have been present.

On this basis and on the discussion during the meeting the following four main points of interest could be drawn up.

1. Dosimetry.
2. Biology of Thorotrast and its carcinogenic effect.
3. Follow up studies.
4. International coordination and collaboration.

In the discussion following this survey. The significance of refined dosimetry was brought up by professor Muth on behalf of the German study group. He summarized the dosimetric questions as follows: In relation to liver tumors it is apart from radiation - non radiation effects the inhomogeneity of the dose distribution which is of interest. Concerning the bone tumors - which so far have not materialised - there are questions concerning Th²³² content of bone, Ra²²⁸/Ra²²⁴ distribution on bone surface and Th²³² distribution ratios in relation to daughters. In general these points were accepted by the following discussion.

The continuation of the follow up studies are necessary. This is especially the case where the national materials so far have been too small to give definitive answers. In these areas an international cooperation is necessary, not only to supply enough material but also to make it possible to transfer data and clinical diagnosis between the groups. The form could not be definitely defined. The different groups are far ahead in their own type of study and may not wish to change the procedure too much as this may introduce serious breaks in the collection of data. However some attempt at more uniformity would be useful. For this purpose some sort of written communication would be necessary. The possibility of data sheets where new information of cases dying, new advances in dosimetry, experiments started etc could be printed for information to the groups was mentioned as one of the possible solutions.

Dr. Seelentag on behalf of WHO outlined a number of further possibilities for collaboration, but a start required some discussion. He suggested that the groups if possible should be

invited to send written suggestions on collaborative procedures to professor Faber for distribution to the participants as basis for further discussion.

The necessity of a protocol for minimal information on the cases was stressed by Rowland. Suggestions for this protocol should be sent to professor Faber. The necessity for coordination in pathology and diagnosis was stressed by Faber, and the difficulties, especially the need for a fairly rigid framework for the collaboration by Dudley. Finally the importance of studying the eventual children from Thorotrast patients was stress by Rowland, Kaick and Tavares.

The possibility for a new meeting was discussed and both Geneva, Lisbon and Heidelberg was suggested as meeting places.

Cases of Bone Tumors in Thorotrast injected Patients,
Portuguese Material, (later informations).

Age at injection	Sex	Amount inj.ml	Latency Period years	Location	Diagnosis confirmed by
19	F	20	29	Femur	clinical + X-ray diagnosis
17	F	24	27	Femur	clinical + X-ray diagnosis
34	M	>60	25	Maxilla	clinical

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